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Dated: November 27, 2013.

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Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2013-N-1523]

Drug Products That Present Demonstrable Difficulties for Compounding Under Sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act; Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification; request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of drug products that present demonstrable difficulties for compounding (difficult-to-compound list). To identify candidates for this list, FDA is encouraging interested groups and individuals to nominate specific drug products or categories of drug products and is describing the information that should be provided to the Agency in support of each nomination.

DATES: Submit written or electronic comments by March 4, 2014.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2013-N-1523, by any of the following methods.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the instructions for submitting comments.

Written Submissions

Submit written submissions in the following ways:

- *Mail/Hand delivery/Courier [for paper submissions]:* Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2013-N-1523 for this request for nominations. All comments

received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Request for Nominations" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Marissa Chaet Brykman, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, suite 5100, Silver Spring, MD 20993-0002, 301-796-3110.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions under which a human drug product compounded for an identified individual patient based on a prescription is entitled to an exemption from three sections of the FD&C Act: (1) Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice for drugs); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)).

One of the conditions for such an exemption is that the compounded drug product is not a "drug product identified by the Secretary 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).

Section 503A(d)(1) of the FD&C Act requires that before issuing regulations to implement section 503A(b)(3)(A) of the FD&C Act, an advisory committee on compounding be convened and consulted "unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health" (section 503A(d)(1) of the FD&C Act).

At a meeting on July 13 and 14, 2000, the Pharmacy Compounding Advisory Committee discussed and provided FDA with advice about the Agency's efforts to develop a list of drugs that present demonstrable difficulties for compounding. FDA had published a notice of that meeting in the **Federal Register** of June 29, 2000 (65 FR 40104). However, before a list could be developed, the constitutionality of section 503A was challenged in court because it 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 held unconstitutional by the U.S. Supreme Court in 2002.¹ After the court decision, FDA suspended its efforts to develop the difficult-to-compound list.

The Drug Quality and Security Act (DQSA) removes from section 503A of the FD&C Act the provisions that had been held unconstitutional by the U.S. Supreme Court in 2002. By removing these provisions, the new law removes uncertainty regarding the validity of section 503A, clarifying that it applies nationwide. Therefore, FDA is reinitiating its efforts to develop a list of drug products that present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product.

In addition, the DQSA adds a new section 503B to the FD&C Act (21 U.S.C. 353b) that creates a new category of "outsourcing facilities." Outsourcing facilities, as defined in section 503B, are facilities that meet certain conditions described in section 503B, including registering with FDA as an outsourcing facility. If these conditions are satisfied, a drug compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility is exempt from two sections of the FD&C Act: (1) Section 502(f)(1) and (2) section 505; but not section 501(a)(2)(B).

One of the conditions in section 503B that must be satisfied to qualify for the exemptions is that an outsourcing facility does not compound a drug identified (directly or as part of a category of drugs) on a list published by the Secretary 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, or the drug is compounded in

¹ See *Thompson v. Western States Med. Ctr.*, 535 U.S. 357 (2002).

accordance with all applicable conditions that are necessary to prevent the drug or category of drugs from presenting such demonstrable difficulties (see section 503B(a)(6)(A) and (a)(6)(B) of the FD&C Act). Section 503B(c)(2) of the FD&C Act requires that before issuing regulations to implement section 503B(a)(6) of the FD&C Act, an advisory committee on compounding be convened and consulted.

FDA intends to develop and publish a single list of drug products and categories of drug products that cannot be compounded and still qualify for any of the exemptions set forth in sections 503A and 503B because they present demonstrable difficulties for compounding.

II. Request for Nominations

To identify candidates for the difficult-to-compound list, FDA is seeking public input in the form of specific drug products or categories of drug products that are difficult to compound. Interested groups and individuals may nominate drug products or categories of drug products that are difficult to compound for inclusion on the list. After evaluating the nominations and, as required by Congress, consulting with the Pharmacy Compounding Advisory Committee (see sections 503A(d)(1) and 503B(c)(2) of the FD&C Act), FDA will issue the list as a regulation under notice-and-comment rulemaking procedures.

Nominations should include the following for each drug product or drug product category nominated, and any other relevant additional information available:

- Name of drug product or drug product category;
- Reason why the drug product or drug product category should be included on the list, taking into account the risks and benefits to patients.

Reasons may include but are not limited to:

- The potential effect of compounding on the potency, purity, and quality of a drug product, which could affect the safety and effectiveness of the drug product. Factors that may be relevant to this determination include:

1. Drug Delivery System

- Is a sophisticated drug delivery system required to ensure dosing accuracy and/or reproducibility?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

2. Drug Formulation and Consistency

- Is a sophisticated formulation of the drug product required to ensure dosing accuracy and/or reproducibility?
- Because of the sophisticated formulation, is product-to-product uniformity of the drug product often difficult to achieve?
- Is the safety or efficacy of the product a concern if there is product-to-product variability?

3. Bioavailability

- Is it difficult to achieve and maintain a uniformly bioavailable dosage form?
- Is the safety or effectiveness of the product a concern if the bioavailability varies?

4. Complexity of Compounding

- Is the compounding of the drug product complex?
- Are there multiple, complicated, or interrelated steps?
- Is there a significant potential for error in one or more of the steps that could affect drug safety or effectiveness?

5. Facilities and Equipment

- Are sophisticated facilities and/or equipment required to ensure proper compounding of the drug product?
- Is there a significant potential for error in the use of the facilities or equipment that could affect drug safety or effectiveness?

6. Training

- Is specialized, highly technical training essential to ensure proper compounding of the drug product?

7. Testing and Quality Assurance

- Is sophisticated, difficult-to-perform testing of the compounded drug product required to ensure potency, purity, performance characteristics, or other important characteristics prior to dispensing?
- Is there a significant potential for harm if the product is compounded without proper quality assurance procedures and end-product testing?
 - Adverse effects that could result when the drug product or drug product category is not made according to appropriate conditions.

FDA cannot guarantee that all drug products or drug product categories nominated during the nomination period will be considered for inclusion on the next published difficult to compound list. Nominations received during the comment period that are supported by the most complete and relevant information will likely be evaluated first. Nominations that are not evaluated during this first phase will

receive consideration for list amendments, because the development of this list will be an ongoing process. Individuals and organizations also will be able to petition FDA to make additional list amendments after the list is published.

Interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set comments. Identify comments with the docket number found in the brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at <http://www.regulations.gov>.

Dated: November 27, 2013.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2013-N-1525]

List of Bulk Drug Substances That May Be Used in Pharmacy Compounding; Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Withdrawal of proposed rule; request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is withdrawing the proposed rule to list bulk drug substances used in pharmacy compounding and preparing to develop a list of bulk drug substances (bulk drugs) that may be used to compound drug products, although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. To identify candidates for this bulk drugs list, interested groups and individuals may nominate specific bulk drug substances, and FDA is describing the information that should be provided to the Agency in support of each nomination.