

TABLE 3—ESTIMATED ANNUAL REPORTING BURDEN ¹

Type of reporting & proposed 21 CFR section	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Notification to FDA that a compounded drug product fails to meet a sterility criterion	10	1	10	5	50

¹ There are no capital costs or operating and maintenance costs associated with this collection of information.

V. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–1525]

Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Revised Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; revised request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of bulk drug substances (active ingredients) that may be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), although they are neither the subject of a United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs. In response to a notice published in the **Federal Register** of December 4, 2013, interested groups and individuals previously nominated a wide variety of substances for this list. However, many of those nominations either were for a substance that is already the subject of a USP monograph or a component of an FDA-approved drug, were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information to justify inclusion of the nominated substance on the list. To improve the efficiency of the process for developing the list of bulk

drug substances that may be used to compound drug products under section 503A, FDA is providing more detailed information on what it needs to evaluate a nomination. Because the deadline for nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances that are not the subject of a USP or NF monograph or a component of an FDA-approved drug. Interested persons will also have the opportunity to provide adequate support to justify placement of the substances on the list. Bulk drug substances that were previously nominated will not be further considered unless they are renominated and those nominations are adequately supported. Substances that are already eligible for use in compounding or that are not adequately supported will not be placed on the list.

DATES: Submit written or electronic nominations for the bulk drug substances list by September 30, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA–2013–N–1525, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

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

Written Submissions

Submit written nominations 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–1525 for this request for nominations. All nominations received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting nominations, 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 nominations 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: Emily Helms Williams, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6280, Silver Spring, MD 20993–0002, 301–796–3381.

SUPPLEMENTARY INFORMATION:

I. Background

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions under which a compounded drug product may be entitled to an exemption from certain sections of the FD&C Act. Those conditions include that the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, that appear on a list developed by the Secretary through regulations issued by the Secretary under subsection (c) of section 503A. See section 503A(b)(1)(A)(i) of the FD&C Act. Under section 503A(c)(2), the criteria for determining which substances should appear on the 503A bulk drugs list “shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify.”

Section 503A refers to the definition of “bulk drug substance” in FDA regulations at § 207.3(a)(4) (21 CFR 207.3(a)(4)). See section 503A(b)(1)(A) of the FD&C Act. As defined in

§ 207.3(a)(4), a “bulk drug substance” is any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.

An “active ingredient” is any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect. See 21 CFR 210.3(b)(7).

Any component other than an active ingredient is an “inactive ingredient.” See 21 CFR 210.3(b)(8). Inactive ingredients used in compounded drug products, which commonly include flavorings, dyes, diluents, or other excipients, need not appear on the Secretary’s list of bulk drug substances to be eligible for use in compounding drug products and will not be included on the list.

In a notice dated November 27, 2013 (the November 27, 2013, notice), published in the **Federal Register** of December 4, 2013 (78 FR 72841), FDA requested nominations for specific bulk drug substances for the Agency to consider placing on the list. In response to that request, 115 comments were submitted to the docket, most of which nominated substances for inclusion on the bulk drug substances list. Some comments nominated several hundred substances, and approximately 10 comments nominated thousands of substances, including en bloc nominations of substances listed in the British Pharmacopeia, the European Pharmacopeia, the Japanese Pharmacopeia, the Food Chemicals Codex, the Homeopathic Pharmacopeia of the United States, and the USP Dietary Supplements Compendium. Several submissions referenced a spreadsheet entitled “OTC Active Ingredients,” available on FDA’s Web site at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf>. Those submissions nominated all of the ingredients on the spreadsheet, which numbered over 1,700 entries.¹

¹ The total number of unique ingredients on the spreadsheet available on FDA’s Web site and the nominations that mirrored that document is lower

However, many of the nominated substances are typically inactive ingredients or foods. Some commonly used inactive ingredients are occasionally used as the active ingredient in a drug product. See 55 FR 46914 at 46916, November 7, 1990 (noting that 21 CFR 310.545 only affects the use of the listed ingredients as active ingredients for the specific indications, and that some of the ingredients listed in the rule, such as sorbitol, sugars, and eucalyptol, have valid uses as inactive ingredients). Ingredients commonly used as inactive ingredients in compounded drug products, such as flavorings, dyes, diluents, or other excipients, need not appear on the Secretary’s list of bulk drug substances to be eligible for use as an inactive ingredient in compounded drug products, should not be nominated, and will not be included on the list. All nominations must demonstrate how the ingredient is used as an active ingredient in a particular compounded drug product.

Additionally, many of the nominated substances are already eligible for use in compounded drug products, namely, those that are components of approved products or are the subject of a USP or NF monograph. Substances that are in one of those two categories need not appear on the list of bulk drug substances to be used in compounded drug products.

Further, many of the nominations did not include sufficient information for the Agency to evaluate whether the substance is appropriate for use in compounded drug products. As stated previously, under section 503A(c)(2) of the FD&C Act, the criteria for determining which substances should appear on the 503A bulk drugs list shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify. Based on this statutory language and prior consultations with the USP and the Pharmacy Compounding Advisory Committee,² FDA is proposing to examine the following four criteria when determining whether a bulk drug substance is appropriate for use in compounded drug products: (1) The physical and chemical characterization of the substance; (2) any safety issues

than this total because the same substances were listed separately for different indications, according to how they are listed in the over-the-counter (OTC) monographs and regulations.

² See 64 FR 996, January 7, 1999 (proposed rule listing bulk drug substances that may be used in pharmacy compounding). This proposed rule was withdrawn in the November 27, 2013, notice but sets forth additional background about the criteria used in the evaluation of nominated bulk drug substances.

raised by the use of the substance in compounded drug products; (3) historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature; and (4) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists. Therefore, to qualify for placement on the list, it is necessary to identify this information about the nominated substances. FDA will evaluate the nominated substances in consultation with the Pharmacy Compounding Advisory Committee.

The November 27, 2013, notice requested that nominations include “[i]nformation about the past and proposed use(s) of the compounded product(s), including the rationale for its use or why the compounded product(s), as opposed to an FDA-approved product, is necessary.” However, many comments to the docket did not provide any information in response to this request. The nominators of the en bloc submissions provided no justification for listing any of the specific substances on the list. To the extent information about the rationale for compounding with a bulk drug substance was provided in individual nominations, many of the comments to the docket included only a brief statement about the use of the compounded drug product and a statement that the product is not available as a commercially made drug. Such statements do not provide sufficient information for FDA to determine whether the nominated bulk drug substance is appropriate for use in compounded drug products. Because the information submitted with previous nominations was insufficient, FDA is unable to determine whether those substances should be included on the list.

To improve the efficiency of the process for developing the list of bulk drug substances that may be used to compound drug products under section 503A, and because the deadline for submitting nominations has passed, FDA is reopening the nomination process so that interested persons have the opportunity to submit nominations of bulk drug substances and provide adequate support for placing them on the list. FDA will be able to evaluate only those bulk drug substances submitted in response to this notice that are supported with adequate data and information, as described in section II.

Bulk drug substances that were previously nominated will not be

further considered unless they are renominated and adequately supported. Substances that are not adequately supported will not be placed on the list. FDA expects the submissions for each bulk drug substance to provide the information described in section II. For example, nominations must include sufficient information to demonstrate that a particular ingredient meets the definition of "bulk drug substance," as defined in § 207.3(a)(4). See section 503A(b)(1)(A) of the FD&C Act. The identification of an ingredient as an "active ingredient" in a regulation, or on a spreadsheet such as the one listing "OTC Active Ingredients," is not sufficient to demonstrate that a substance is a bulk drug substance for purposes of the 503A list. En bloc nominations of substances listed in compendia, pharmacopeia, or similar reference materials cannot be placed on the list unless the Agency receives adequate information for each bulk drug substance to justify its placement on the list. FDA will only be able to consider bulk drug substances that are supported with the information requested.

In section II, FDA identifies the type of information needed to support a nomination to the 503A list.

II. Request for Nominations

Interested groups and individuals may nominate specific bulk substances for inclusion on the list. Nominations will only be evaluated if they are for specific active ingredients that meet the definition of a bulk drug substance in § 207.3(a)(4), are not for components of approved products, and are not for the subject of a USP or NF monograph. To fully evaluate a bulk drug substance, FDA needs the following information about both the bulk drug substance being nominated and the drug product(s) that will be compounded using such substance:

A. Confirmation That the Nominated Substance Is a Bulk Drug Substance and Is Not Already Eligible for 503A Compounding

- A statement that the nominated substance is an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4), and an explanation of why the substance is

considered an active ingredient when it is used in the identified compounded drug product(s), citing to specific sources that describe the active properties of the substance.

- A statement that the nominator has searched for the active ingredient in all three sections of the Orange Book (for prescription drug products, over-the-counter drug products, and discontinued drug products), available at <http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm>, and the drug substance did not appear in any of those searches, confirming that the substance is not a component of any FDA-approved product.

- A statement that the nominator has searched USP and NF monographs, available at <http://www.uspnf.com>, and the drug substance is not the subject of such a monograph.

B. General Background on the Bulk Drug Substance

- Ingredient name;
- Chemical name;
- Common name(s);
- Identifying codes, as available, from FDA's Unique Ingredient Identifiers (UNII) used in the FDA/USP Substance Registration System, available at <http://fdasis.nlm.nih.gov/srs/>. Because substance names can vary, this code, where available, will be used by the Agency to confirm the exact substance nominated and to identify multiple nominations of the same substance so the information can be reviewed together.

- Chemical grade of the ingredient;
- Description of the strength, quality, stability, and purity of the ingredient;
- Information about how the ingredient is supplied (e.g., powder, liquid); and
- Information about recognition of the substance in foreign pharmacopeias and the status of its registration(s) in other countries, including whether information has been submitted to USP for consideration of monograph development.

C. Information on the Drug Product That Will Be Compounded With the Bulk Drug Substance

- Information about the dosage form(s) into which the bulk drug substance will be compounded;

- Information about the strength(s) of the compounded drug product(s);

- Information about the anticipated route(s) of administration of the compounded product(s);

- A bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available,³ including any relevant peer-reviewed medical literature; and

- Information about the past and proposed use(s) of the compounded drug product(s), including the rationale for its use and why the compounded product(s), as opposed to an FDA-approved product, is necessary. Information on the rationale for use of the bulk drug substance and why a compounded drug product is necessary must be specific to the compounded drug product at issue. General or boilerplate statements regarding the need for compounded drug products or the benefits of compounding generally will not be considered sufficient to address this issue.

D. Nomination Process

Because the deadline for submitting nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances and have the opportunity to provide adequate support for placing them on the list. Bulk drug substances that were previously nominated need to be renominated. Nominators are encouraged to submit as much of the information identified in this document as possible. Unless adequate supporting data is received for a bulk drug substance, FDA will be unable to consider it further for inclusion on the list. Individuals and organizations will be able to comment on nominated substances after the nomination period has closed or petition FDA to make additional list amendments after the list is published, in accordance with 21 CFR 10.30.

For efficient consolidation and review of nominations, nominators are encouraged to submit their nominations in an editable Excel file. Specifically, nominators are encouraged to format their nominations as follows:

Column A—What information is requested?	Column B—Put data specific to the nominated substance
What is the name of the nominated ingredient?	Provide the ingredient name.
Is the ingredient an active ingredient that meets the definition of "bulk drug substance" in § 207.3(a)(4)?	Provide an explanation for why it is considered an active ingredient when it is used in specific compounded drug products, and provide citations to specific sources that describe its active properties.

³ FDA recognizes that the available safety and efficacy data supporting consideration of a bulk

drug substance for inclusion on the list may not be

of the same type, amount, or quality as is required to support a new drug application.

Column A—What information is requested?	Column B—Put data specific to the nominated substance
Is the ingredient listed in any of the three sections of the Orange Book?	Confirm whether the ingredient is a component of an FDA-approved product.
Were any monographs for the ingredient found in the USP or NF monographs?	Confirm whether the ingredient is the subject of a USP or NF monograph.
What is the chemical name of the substance?	Chemical name.
What is the common name of the substance?	Common name.
Does the substance have a UNII Code?	UNII code.
What is the chemical grade of the substance?	Provide the chemical grade.
What is the strength, quality, stability, and purity of the ingredient?	Provide the strength, quality, stability, and purity information.
How is the ingredient supplied?	Describe how the ingredient is supplied (e.g., powder, liquid).
Is the substance recognized in foreign pharmacopeias or registered in other countries?	List the foreign pharmacopeias or other countries in which it is registered.
Has information been submitted about the substance to the USP for consideration of monograph development?	Put yes, no, or unknown. If yes, state the status of the monograph, if known.
What dosage form(s) will be compounded using the bulk drug substance?	State the dosage form(s).
What strength(s) will be compounded from the nominated substance?	List the strength(s) of the drug product(s) that will be compounded from the nominated substance, or a range of strengths, if known.
What are the anticipated route(s) of administration of the compounded drug product(s)?	List the route(s) of administration of the compounded drug product(s).
Are there safety and efficacy data on compounded drugs using the nominated substance?	Provide a bibliography of safety and efficacy data for the drug compounded using the nominated substance, if available, including any relevant peer-reviewed medical literature.
Has the bulk drug substance been used previously to compound drug product(s)?	Describe past uses of the bulk drug substance in compounding.
What is the proposed use for the drug product(s) to be compounded with the nominated substance?	Provide information on the proposed use of the compounded drug product.
What is the reason for use of a compounded drug product rather than an FDA-approved product?	Provide a rationale for the use of a compounded drug product.
Is there any other relevant information?	Provide any other information you would like FDA to consider in evaluating the nomination.

Interested persons may submit either electronic nominations to <http://www.regulations.gov> or written nominations to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of nominations. Identify nominations with the docket number found in the brackets in the heading of this document. Received nominations 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: June 25, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2013-N-1524]

Bulk Drug Substances That May Be Used To Compound Drug Products in Accordance With Section 503B of the Federal Food, Drug, and Cosmetic Act, Concerning Outsourcing Facilities; Revised Request for Nominations

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; revised request for nominations.

SUMMARY: The Food and Drug Administration (FDA or Agency) is preparing to develop a list of bulk drug substances (active ingredients) that may be used to compound drug products in accordance with section 503B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) concerning outsourcing facilities. In response to a notice published in the **Federal Register** of December 4, 2013, interested groups and individuals previously nominated a wide variety of substances for this list. However, many of those nominations were not for bulk drug substances used in compounding as active ingredients, and none included sufficient information to justify inclusion of the

nominated substances on the list. To improve the efficiency of the process for developing the list of bulk drug substances that may be used to compound drug products under section 503B of the FD&C Act, FDA is providing more detailed information on what it needs to evaluate a nomination. Because the deadline for nominations has passed, FDA is reopening the nomination process so that interested persons can submit nominations of bulk drug substances and provide adequate support to justify placing the substances on the list. Bulk drug substances that were previously nominated will not be further considered unless they are renominated and adequately supported. Substances that are not adequately supported will not be placed on the list.

DATES: Submit written or electronic nominations for the bulk drug substances list by September 30, 2014.

ADDRESSES: You may submit nominations, identified by Docket No. FDA-2013-N-1524, by any of the following methods.

Electronic Submissions

Submit electronic nominations in the following way:

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