4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-N-3534]

Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; establishment of public docket

SUMMARY: The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances (active ingredients) that can be used to compound drug products in accordance with the Federal Food, Drug, and Cosmetic Act (the FD&C Act), although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs (503A bulks list). The Agency previously solicited nominations for the list, but some of the nominated substances were not supported by sufficient information for FDA to evaluate them. FDA is establishing a public docket where these substances can be renominated with sufficient supporting information or to receive nominations of bulk drug substances that were not previously nominated for consideration for inclusion on the 503A bulks list. Interested parties can also submit comments on nominated substances via this docket.

DATES: Nominations and comments may be submitted to this docket at any time.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to http://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on http://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2015-N-3534 for "Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act; Establishment of a Public Docket." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at http://www.regulations.gov or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on http://www.regulations.gov. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: http://www.fda.gov/regulatoryinformation/dockets/default.htm.

Docket: For access to the docket to read background documents or the electronic and written/paper 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: Philantha Bowen, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 5175, Silver Spring, MD 20993-0002, 301-796-2466.

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 a licensed pharmacist in a State licensed pharmacy or Federal facility or a 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) of the FD&C Act, the criteria for determining which substances should appear on the 503A bulks 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 invited 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. Over 2,000 substances were nominated. However, many of the nominations were for substances that can be used for compounding without being on the list because they are the subject of an applicable USP or NF monograph or

are a component of an FDA-approved drug. In addition, many of the nominations were not for bulk drug substances used in compounding as active ingredients, or did not include sufficient information to allow FDA to evaluate the substance for inclusion on the list. To improve the efficiency of the process for developing the 503A bulks list, FDA reopened the nomination process in July 2014 (79 FR 37742, July 2, 2014) and provided more detailed information on what it needs to evaluate nominations for the list. FDA stated that bulk drug substances that were previously nominated would not be considered further unless they were re-nominated with adequate support to permit a meaningful evaluation. Substances that were already eligible for use in compounding or that were not adequately supported would not be evaluated for placement on the list.

In response to the July 2, 2014, request for nominations, approximately 740 unique substances were nominated. Of the nominated substances, approximately 275 are already eligible for use in compounding because they are either components of an approved drug or the subject of an applicable USP or NF monograph. At least nine of the nominated substances are not eligible for inclusion on the list because they are either a finished drug product, a biological product subject to licensure in a biologics license application (BLA), a radiopharmaceutical drug product, a substance with no currently accepted medical use that is included on Schedule I of the Controlled Substances Act (21 U.S.C. 812(c)), or they appear on the list published by FDA of substances 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. Of the substances that are not components of an FDA-approved drug or the subject of an applicable USP or NF monograph, not biological products subject to licensure in a BLA, not radiopharmaceuticals, do not appear on Schedule I, and do not appear on the withdrawn or

removed list, approximately 390 substances were nominated with insufficient supporting evidence for FDA to evaluate them.

II. Establishment of a Docket

As described in section III.B of the draft guidance entitled, "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act," FDA is establishing a public docket so that interested parties can comment on nominated bulk drug substances, nominate bulk drug substances that were not previously nominated for the 503A bulks list, or renominate with adequate supporting information bulk drug substances that were previously nominated but that were not supported by sufficient information for FDA to evaluate them. Docket No. FDA-2013-N-1525 is closed for comment. Therefore, this new docket can be used for commenting on nominations submitted to that docket as well as for submitting new nominations.

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 consultations with the USP and the Pharmacy Compounding Advisory Committee (PCAC),[1] FDA is considering the use of the following four criteria to determine whether a bulk drug substance is appropriate for use in compounding: (1) The physical and chemical characterization of the substance; (2) any safety issues 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

[1] 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. The criteria were discussed with the PCAC, the membership of which includes a USP representative, at its meeting on February 22, 2015.

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 be considered for placement on the 503A bulks list, this information should be submitted for each nominated substance. FDA will evaluate the nominated substances in consultation with the USP and the PCAC.

Interested groups and individuals may nominate specific bulk drug substances for inclusion on the 503A bulks list, renominate previously nominated substances with additional information, or comment on nominated substances. Nominations will only be evaluated if they are for specific active ingredients that: (1) Meet the definition of a bulk drug substance in § 207.3(a)(4); (2) are not components of FDA-approved drug products; and (3) are not substances that are the subject of an applicable USP or NF monograph. To fully evaluate a bulk drug substance using the criteria identified above, FDA needs the following information about both the nominated bulk drug substance 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 applicable USP and NF drug 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, and a copy of a certificate of analysis that is representative of the characteristics of the nominated 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 the 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,[2] 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. Process for Submitting Nominations and Comments

Because the prior deadline for submitting nominations has passed, FDA is opening this docket so that interested persons can submit nominations of bulk drug substances and provide adequate support for FDA to evaluate whether those substances should be placed on the 503A bulks list. Bulk drug substances that were previously nominated and for which inadequate

[2] 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.

information was provided[3] need to be renominated with the information identified above to be considered for inclusion on the 503A bulks list. 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.

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
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 drug monographs for the ingredient found in the USP or NF monographs?	Confirm whether the ingredient is the subject of an applicable 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 and attach a certificate of analysis.
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 drug 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)

[3] As referenced above, a list of the substances in this category is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM467373.pdf.

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

In addition to nominating new substances or renominating substances previously nominated without sufficient supporting information, individuals and organizations will be able to comment via the docket established by this notice on substances nominated for the 503A bulks list that have not yet been addressed in a Notice of Proposed Rulemaking (NPRM). Comments may be submitted regarding nominations submitted to both this docket and Docket No. FDA-2013-N-1525. Comments may provide any relevant information about particular bulk drug substances, including that in support of, or in opposition to, the placement of a nominated bulk drug substance on the 503A bulks list. However, comments submitted should not address the 503A bulks list generally or other matters related to the Agency's regulation of compounding. Comments about nominated substances that have been addressed by the Agency in an NPRM should be submitted to the docket for the proposed rulemaking in which the substance is addressed.

Please do not submit comments that have already been submitted to other dockets. Such submissions are duplicative and not helpful to the Agency. If comments on particular documents or issues are submitted to this docket rather than the docket specifically opened for the particular document or issue, the comment might not be considered as the specific documents are being finalized and issues considered. FDA will not respond to questions submitted to this docket.

Information in the docket will be publicly available. Therefore, we remind nominators and commenters not to submit personal or confidential information.

Dated: October 21, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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