Section 503A Bulks List Final Rule Questions and Answers

Guidance for Industry

(Small Entity Compliance Guide)

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

May 2019

Compounding

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Contains Nonbinding Recommendations

Section 503A Bulks List Final Rule Questions and Answers Guidance for Industry[1]

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I. INTRODUCTION

This guidance is intended to help small businesses better understand and comply with the final rule establishing the list of bulk drug substances[2] that can be used in compounding under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) (final rule or 503A Bulks List Final Rule). On February 19, 2019 (84 FR 4696), FDA published a final rule that establishes FDA's criteria for evaluating bulk drug substances for inclusion on the list of bulk drug substances that may be used to compound drug products under section 503A of the FD&C Act (the 503A Bulks List or the list) and that places six substances on the list. The final rule, entitled "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," also identifies four substances that were considered for and not included on the list.

The 503A Bulks List Final Rule is effective March 21, 2019. FDA has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121, as amended by Public Law 110-28)[3] to assist small businesses in complying with the 503A Bulks List Final Rule.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances 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 Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Office of Regulatory Policy and the Office of Unapproved Drug Labeling Compliance in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] FDA is evaluating bulk drug substances nominated for the 503A Bulks List on a rolling basis and intends to address additional substances in future rulemaking.
[3] 5 U.S.C. 601.

II. BACKGROUND

Section 503A of the FD&C Act describes the conditions under which a compounded drug product qualifies for exemptions from certain requirements of the FD&C Act related to FDA approval prior to marketing, current good manufacturing practice requirements, and labeling with adequate directions for use. One of the conditions that must be met for a compounded drug product to qualify for these exemptions is 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 United States Pharmacopeia (USP) or National Formulary 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 FDA; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by FDA, appear on a list of bulk drug substances developed by FDA through regulation.[4]

As noted above, the 503A Bulks List Final Rule establishes criteria for evaluating bulk drug substances for inclusion on the 503A Bulks List, identifies six bulk drug substances FDA is placing on the list, and identifies four other bulk drug substances that were considered and are not being included on the 503A Bulks List.

III. QUESTIONS AND ANSWERS

Q1. What active ingredients are subject to this final rule?

The 503A Bulks List Final Rule addresses only 10 of the substances nominated for the 503A Bulks List. The final rule identifies six bulk drug substances FDA is placing on the list: Brilliant Blue G, also known as Coomassie Brilliant Blue G-250; cantharidin (for topical use only); diphenylcyclopropenone (for topical use only); N-acetyl-D-glucosamine (NAG) (for topical use only); squaric acid dibutyl ester (for topical use only); and thymol iodide (for topical use only). The final rule also identifies four other bulk drug substances that are not being included on the list: oxitriptan, piracetam, silver protein mild, and tranilast.

Although only the 10 substances listed above are specifically addressed in the final rule, the criteria for evaluation identified in the final rule will be applied to all bulk drug substances that are considered for the 503A Bulks List.

Q2. Can substances that have been considered and not placed on the 503A Bulks List through a final rule be used in compounding under 503A?

No. As stated above, section 503A provides compounded drug products with exemptions from certain requirements of the FD&C Act, including premarket approval, but only when those compounded drug products meet the conditions of section 503A. A compounded drug product that includes one of the four bulk drug substances that are not being placed on the list would not meet those conditions and therefore would not qualify for the exemptions from the FD&C Act.

[4] See section 503A(b)(1)(A)(i) of the FD&C Act (21 U.S.C. 353a(b)(1)(A)(i)).

In addition, as described in the *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance for Industry*,[5] substances that have been evaluated and not placed on the 503A Bulks List no longer qualify for the interim policy concerning compounding with bulk drug substances.

Q3. What should I do if I am a pharmacist and I receive a prescription for a compounded drug product that includes one of the four bulk drug substances that is not being placed on the 503A Bulks List as part of this final rule?

A drug product compounded using a bulk drug substance that is identified in a final rule as not being placed on the 503A Bulks List does not qualify for the exemptions under section 503A of the FD&C Act. Compounding with any of the four substances identified in the 503A Bulks List Final Rule, or with substances identified in any other final rule as not being placed on the 503A Bulks List, may subject the compounder to regulatory action.

Q4. When and how do compounders have to comply with this final rule?

The 503A Bulks List Final Rule is effective March 21, 2019. As of that date, drug products compounded using any of the four bulk drug substances that are identified as not being included on the list do not qualify for the exemptions under 503A of the FD&C Act. Drug products compounded using one of the six bulk drug substances that are on the list will qualify for the exemptions under section 503A of the FD&C Act provided the drug products are compounded in compliance with the other conditions of section 503A of the FD&C Act.

Q5. Going forward, how will FDA decide whether to place a bulk drug substance on the 503A Bulks List?

As described in the final rule, FDA is evaluating nominated bulk drug substances using four criteria: the physical and chemical characteristics of the substance, the safety of the substance in compounded drug products, evidence of effectiveness, and historical use of the substance in compounded drug products. As required by section 503A of the FD&C Act, FDA is consulting with the Pharmacy Compounding Advisory Committee (PCAC) and USP regarding the 503A Bulks List and is developing the list through notice and comment rulemaking.

Q6. Why did FDA find the four substances it is not placing on the 503A Bulks List to be inappropriate for use in compounding drug products under section 503A of the FD&C Act?

For reasons described at length in the proposed rule that published on December 16, 2016 (81 FR 91071), entitled "List of Bulk Drug Substances That Can Be Used To Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," and in the briefing materials presented to the PCAC, applying the four criteria identified in Question 5 above, FDA determined that these four substances are not appropriate for use in compounding drug products under section 503A of the FD&C Act.

[5] We update guidances periodically. To make sure you have the most recent version of a guidance, be sure to check the Agency's guidance website at http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm.

Q7. What information did FDA rely on to make its determinations for the bulk drug substances that are addressed in the final rule?

As stated in the December 16, 2016 proposed rule, FDA considered information obtained from publicly available sources, including peer-reviewed medical literature. Some of this information was referenced in the nominations, and the remainder FDA gathered through independent searches of medical and pharmaceutical databases. FDA did not review raw data. The nature, quantity, and quality of the information FDA assessed varied considerably from substance to substance. In some cases, there were very little data. For other substances, reports in the literature were more plentiful and sometimes comprised hundreds or thousands of articles. In those cases, generally, the Agency limited its review to a sample of the best literature sources available (e.g., review articles in widely known, peer-reviewed journals; meta-analyses; reports of randomized controlled trials).

Q8. What should I do if I want to use one of the four bulk drug substances that has been identified in the final rule as not being placed on the list to compound a route of administration or dosage form different than what the bulk drug substance was nominated and considered for when it was determined that it would not be placed on the list (e.g., the bulk drug substance was considered in the context of compounding an injectable drug product, but I want to use it to compound a tablet)?

If you would like to compound a drug product using a bulk drug substance identified as not placed on the list, you may submit a citizen petition under 21 CFR 10.30. The petition should ask FDA to consider revising the rule to include the bulk drug substance. The petition should explain any differences in how you propose to use the bulk drug substance as compared with how it was previously nominated and evaluated for inclusion on the list.

Q9. Does FDA plan to add additional substances to the 503A Bulks List going forward?

Many substances have been nominated for the 503A Bulks List, and FDA has been evaluating them on a rolling basis. FDA intends to publish additional notice and comment rulemaking to address whether these substances should be included on the list.

Q10. Where can I get more information, if needed?

Questions regarding compliance with the 503A Bulks List Final Rule should be directed to Compounding@fda.hhs.gov.