



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 216

[Docket No. FDA-2016-N-3464]

RIN 0910-AH29

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing a final rule to establish criteria for and identify an initial list of bulk drug substances that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (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. Specifically, the Agency is placing six bulk drug substances on the list. This final rule also identifies four bulk drug substances that FDA has considered and is not including on the list. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of a future rulemaking.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this final rule into the “Search” box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Rosilend Lawson, Center for Drug Evaluation and Research, Office of Unapproved Drugs and Labeling Compliance, Food and Drug Administration, 10903 New Hampshire Ave, Bldg. 51, Rm. 5197, Silver Spring, MD 20993, 240-402-6223, Rosilend.Lawson@fda.hhs.gov.

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I. Executive Summary

A. Purpose of the Final Rule

FDA is amending title 21 of the Code of Federal Regulations to add a list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (referred to as “the 503A Bulks List” or “the list”). Bulk drug substances that appear on the 503A Bulks List can be used to compound drug products subject to the conditions of section 503A, although those substances are not the subject of an applicable USP or NF monograph or components of approved drug products.

B. Summary of the Major Provisions of the Final Rule

In this final rule, FDA is establishing the criteria for evaluation of bulk drug substances for inclusion on the 503A Bulks List: (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) the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and (4) 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.

Based on the results of its evaluation of nominated bulk drug substances to date, as well as consultation with the Pharmacy Compounding Advisory Committee (PCAC) and USP, FDA is including six bulk drug substances 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). FDA is also identifying four other bulk drug substances that will not be included on the list: oxitriptan, piracetam, silver protein mild, and tranilast. Drugs compounded with these substances will not qualify for the 503A exemptions and cannot be used in compounding under section 503A of the FD&C Act.

C. Legal Authority

Section 503A, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serves as our principal legal authority for this final rule.

D. Costs and Benefits

FDA is establishing criteria for evaluating inclusion of bulk drug substances on the 503A Bulks List, placing six bulk drug substances on the 503A Bulks List, and not including four bulk drug substances on the 503A Bulks List. The present value of the costs of the final rule equals \$3.33 million at a 7 percent discount rate and \$3 million at a 3 percent discount rate. The final rule will result in annualized costs of \$0.42 million at a 7 percent discount rate, or \$0.31 million at a 3 percent discount rate. Because we lack sufficient information to quantify many of the costs and the benefits of this final rule, we also include a qualitative description of potential benefits and potential costs. We expect that the rule would affect compounding pharmacies and

certain other entities that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected drug substances, and payers that cover these drug products or alternative drug products.

II. Table of Abbreviations/Commonly Used Acronyms in This Document

Abbreviation/Acronym	What It Means
APA	Administrative Procedure Act
5-HTP	5-hydroxytryptophan
CFR	Code of Federal Regulations
DQSA	Drug Quality and Security Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
FDA	Food and Drug Administration
GRAS	Generally recognized as safe
HPUS	Homeopathic Pharmacopeia of the United States
IND	Investigational new drug
NAG	N-acetyl-D-glucosamine
NDA	New drug application
NF	National Formulary
NPRM	Notice of proposed rulemaking
OTC	Over-the-counter
PCAC	Pharmacy Compounding Advisory Committee
PDUFA	Prescription Drug User Fee Act
USP	United States Pharmacopeia

III. Background

A. Need for and History of This Rulemaking

Section 503A describes the conditions under which a compounded drug product qualifies for exemptions 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 of Health and Human Services (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 the 503A Bulks List. (See section 503A(b)(1)(A)(i) of the FD&C Act.) This final rule establishes criteria for evaluating bulk drug substances for inclusion on the 503A Bulks List and identifies six bulk drug substances the Secretary is placing on the list. The Agency considered four other bulk drug substances and is not including those substances on the 503A Bulks List. Additional bulk drug substances are under evaluation, and new substances may be added to the list through subsequent rulemaking.

The definitions that are relevant to this final rule are set forth in the notice of proposed rulemaking (NPRM) published in the *Federal Register* of December 16, 2016 (81 FR 91071). The 2016 proposed rule also includes a complete history of this rulemaking. In that proposed rule, FDA discussed the 10 bulk drug substances nominated for inclusion on the 503A Bulks List that are the subject of this final rule, along with the criteria FDA proposed to use when determining whether to place bulk drug substances on the 503A Bulks List.

Under this final rule, drug products compounded with the six substances that are being placed on the 503A Bulks List qualify for the 503A exemptions if the conditions of section 503A of the FD&C Act are met. In contrast, drugs compounded with the other four substances evaluated in this rulemaking--which are not being placed on the 503A Bulks List-- do not qualify for the 503A exemptions and cannot be used in compounding under section 503A of the FD&C Act. As discussed in the 2016 proposed rule and in the guidance for industry entitled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act" (Interim Policy Guidance) (Ref. 1), FDA generally has not intended to take regulatory action for the use of certain substances, including the 10 substances that are the subject of this final rule, while those substances were being considered for inclusion on the 503A

Bulks List (interim policy). Since the rulemaking is now complete for these 10 nominated substances, the interim policy no longer applies to those substances.

B. Summary of Comments to the Proposed Rule

We received eight substantively relevant, unique comments to the 2016 proposed rule. The comments addressed FDA's proposals on the criteria for evaluating bulk drug substances for inclusion on the 503A Bulks List, including some comments on how FDA has been using the criteria in practice. The comments also addressed FDA's proposals on particular bulk drug substances. In addition to these topics, which addressed the language proposed to be included in the Code of Federal Regulations (CFR), commenters addressed a variety of topics related to FDA's evaluation of bulk drug substances, including procedural issues related to meetings of the PCAC, and compounding policies generally.

IV. Legal Authority

As described in the Background section, section 503A describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from three sections of the FD&C Act (sections 501(a)(2)(B), 502(f)(1), and 505 (21 U.S.C. 351(a)(2)(B), 352(f)(1), and 355)). One of the conditions that must be satisfied for a compounded drug to qualify for the exemptions under section 503A of the FD&C Act is that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounding drug products using bulk drug substances, must use 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, appear on the 503A Bulks List. (See section 503A(b)(1)(A)(i) of the FD&C Act.) Section 503A(c)(1) of the FD&C Act also states that the Secretary shall issue regulations to implement certain parts of section 503A, and that before issuing regulations to implement section 503A(b)(1)(A)(i)(III) pertaining to the 503A Bulks List, among other sections, the Secretary shall convene and consult an advisory committee on compounding unless the Secretary determines that the issuance of such regulations before consultation is necessary to protect the public health. Section 503A(c)(2) of the FD&C Act requires the Secretary to issue the regulations in consultation with the USP, and to include in the regulation the criteria for such substances that shall include historical use, reports in peer-reviewed journals, and any other criteria the Secretary identifies. Thus, section 503A of the FD&C Act, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serves as our principal legal authority for this final rule.

V. Comments on the Proposed Rule and FDA Response

A. Introduction

We received 12 total comments posted to the docket for the proposed rule by the close of the comment period. Of the 12 comments received, 3 addressed subjects other than the proposed rule, and 9 were related to the proposed rule. Of the nine comments substantively related to the proposed rule, one was a duplicate. Of the eight unique, substantively relevant comments received, each discussed one or more issues. We received comments from consumers; trade organizations, including those representing compounders and clinicians with particular specialties; a company that sells bulk drug substances and other materials for compounding; and other organizations.

We describe and respond to the issues raised in the comments in sections V.B. and V.C. of this document. We have consolidated and grouped the issues raised in the comments, and assigned each issue a “comment number” to help distinguish among different issues raised in the comments. We have grouped similar issues raised in the comments together under the same comment number, and, in some cases, we have separated different issues discussed in the same comment and designated them with distinct comment numbers for purposes of our responses. The comment number assigned to each issue or topic is purely for organizational purposes and does not signify the value or importance of the issue or the order in which comments were received.

We received some comments that raised issues that are outside the scope of this rulemaking (e.g., animal testing, access to compounded drug products as “office stock,” FDA’s interpretation of the phrase “clinical need” as used in section 503B of the FD&C Act, competition and drug pricing). To the extent issues raised in comments are unrelated to this rulemaking, we do not respond to those comments.

B. Description of General Comments and FDA Response

(Comment 1) Some comments made general remarks supporting the proposed rule. These comments supported the proposed criteria, the proposed placement of the six substances listed above on the 503A Bulks List, the proposal not to include the four substances listed above on the 503A Bulks List, and FDA’s Interim Policy Guidance.

(Response 1) We appreciate the support expressed in the comments received.

C. Specific Comments and FDA Response

1. Proposed Criteria

(Comment 2) Some comments objected to the proposed criteria as too broad and vague to provide standards by which ingredients will be judged. For example, one comment stated that FDA fails to define what constitutes “significant” toxicity or “other safety concerns,” which are vague and give FDA too much discretion. The comments stated that the proposed criteria will lead to highly subjective decisions.

(Response 2) We disagree and find no basis to change the criteria proposed in the 2016 proposed rule based on this comment. We acknowledge that the criteria have been and will be applied on a substance-by-substance basis, given the risks and benefits that may be presented by a particular substance. The Agency believes some measure of flexibility is necessary for FDA to evaluate the nominated bulk drug substances. We have applied and will continue to apply the criteria consistently, weighing them as appropriate based on the nature of the substance and proposed use, among other things. FDA also notes that its application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and also is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not applying the criteria correctly in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 3) One commenter objected to the fourth criterion FDA proposed in the 2016 proposed rule: “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.” The commenter explained that current use is more relevant than historical use.

(Response 3) We disagree that FDA should not consider historical use. Further, we note that consideration of current use is encompassed in the historical use criterion. Regarding the criteria used to determine whether a bulk drug substance should be placed on the 503A Bulks List, section 503A(c)(2) of the FD&C Act specifies that the criteria shall include historical use, reports in peer reviewed medical literature, or other criteria the Secretary may identify. We are, therefore, required by statute to consider the historical use of a bulk drug substance. As we explained in the 2016 proposed rule, the Agency is considering how widespread the use of a bulk drug substance has been, as well as references in peer-reviewed medical literature, as part of the evaluation of the historical use.

(Comment 4) One commenter objected to FDA’s consideration of the historical use criterion, noting that FDA has not been giving this factor adequate weight. This commenter suggested that, instead of applying the criterion as proposed, FDA should recommend a bulk drug substance for the 503A Bulks List if it has historically been in significant use by a particular specialty or community of physicians unless there is reliable evidence that the ingredient presents unacceptable sterility concerns or potential for adverse reactions.

(Response 4) As noted above, FDA is statutorily required to consider historical use when evaluating the nominated bulk drug substances, and the Agency has been doing so. To the extent information pertaining to historical use has been available, it has been discussed at length in each of the reviews underlying FDA’s recommendations to the PCAC and its proposals in the 2016 proposed rule. As noted above, each criterion may weigh differently in the context of the risks and benefits presented by a particular bulk drug substance, and historical use may weigh more

heavily in some cases than others. As also stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not giving the historical use criterion adequate weight in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance from the 503A Bulks List. We decline to adopt the commenter's suggestion to consider historical use as dispositive in certain cases, as we believe doing so would give disproportionate weight to the historical use criterion and would not give adequate consideration to a substance's physical and chemical characterization, safety, or effectiveness.

(Comment 5) Some commenters objected to FDA's consideration of the availability of approved drug products or drug products that conform to an over-the-counter (OTC) monograph to treat the same condition as the proposed bulk drug substance, and proposed that these alternatives not weigh against inclusion of the substance on the 503A Bulks List. The commenters noted that drug products are compounded because the drugs already available are not appropriate or effective for individual patients. Further, the commenters opposed the consideration of alternative therapies because they assert FDA has failed to consider the side effects of FDA-approved products, and any concern that use of compounded drugs could delay use of approved products is baseless. One of the commenters suggested that the approved alternatives should only be considered where the approved medication leads to a complete cure or remission of illness or otherwise fully addresses the purpose intended for the compounded drug product, and there is no other reason a compounded drug product containing the nominated bulk drug substance should be available.

(Response 5) We disagree with this comment and believe that the existence of FDA-approved drug products or drug products that conform to an OTC monograph may be relevant in the evaluation of particular bulk drug substances. However, the existence of alternative therapies is not one of the four criteria FDA is using to evaluate nominated bulk drug substances, nor is the availability of approved alternatives dispositive when considering whether to add a substance to the list. Rather, as explained in the 2016 proposed rule, we consider the existence of FDA-approved or OTC-monograph drug products relevant to FDA's consideration of the safety criterion, to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the effectiveness criterion, to the extent there may be alternative therapies that have been demonstrated to be effective for certain conditions. Therefore, we find no reason to exclude consideration of the existence of FDA-approved or OTC monograph drug products where relevant.

Regarding the comment that FDA has not adequately considered the side effects of alternative therapies, we disagree and have considered the side effects of alternative therapies as part of the safety criterion where information is available and relevant. We note, however, that data comparing the safety profiles of compounded drug products with approved drug products are generally not available. In fact, in many cases, there are minimal data available concerning the safety, including side effects, of compounded drugs. The absence of information does not mean that safety risks do not exist. In contrast, approved drug products have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the benefits of the drug product for the approved conditions of use have been found to outweigh the risks. Similarly, regarding effectiveness, often there are minimal data supporting the effectiveness of a compounded drug product, and it may be preferable for a patient to use a drug product with side

effects when that drug product has been proven to be effective. Even if a compounded drug product has fewer side effects than an FDA-approved or OTC monograph drug product, if it does not treat the condition at issue, it may be of no or limited benefit to the patient.

Regarding the comment that approved alternatives should only be considered when there is evidence that the FDA-approved drug product or OTC monograph product fully addresses patients' needs, we disagree. While not one of the four criteria, as described in the 2016 proposed rule and reflected in reviews completed and presented to the PCAC, under certain circumstances, the existence of an approved drug product or OTC monograph product to treat the condition, even where the product may not fully address patients' needs, is relevant to FDA's evaluation of one or more of the four criteria. For example, in considering the effectiveness criterion, the existence of an approved drug product or OTC monograph product may weigh against placing a substance on the 503A Bulks List when the condition to be treated is very serious or life threatening because of the serious consequences that could result from use of an ineffective or less effective treatment alternative (2016 proposed rule, 81 FR 91071 at 91075.) Likewise, in considering the safety criterion, the existence of an approved drug product or OTC monograph product likely would weigh against placing a substance on the 503A Bulks List when the toxicity of the substance appears to be significant, or other safety concerns are associated with the use of the substance (*id.*).

Further, we note that, as stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not adequately considering the side effects of FDA-approved products in any

particular case, the Agency will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 6) One commenter proposes that a substance should be added to the 503A Bulks List if the Center for Food Safety and Applied Nutrition (CFSAN) has determined the substance is generally recognized as safe (GRAS).¹

(Response 6) We disagree. GRAS determinations for food are made under food safety standards and thus are not dispositive when considering the use of a substance as an active ingredient in a compounded drug product. A substance that is safe when used as a food might not be safe as an active ingredient in a drug product, for example, when used for a route of administration other than oral. Moreover, such a GRAS determination does not indicate that a substance would have any effectiveness for a particular proposed use when used in a compounded drug product. We note, however, that FDA has considered CFSAN's GRAS notices and their implications in reviews completed to date where relevant, for example, in our review of safety or physical and chemical properties.

As stated above, FDA's application of the criteria to particular substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it is not adequately considering the GRAS determination of a substance in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

¹ Under sections 201(s) and 409 of the FD&C Act (21 U.S.C. 321(s) and 348), any substance that is intentionally added to food is a food additive that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excepted from the definition of a food additive. For more information, see <https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/>.

(Comment 7) One comment objected to FDA's consideration of the seriousness of the condition the drug product compounded with the nominated bulk drug substance is proposed to treat. In the 2016 proposed rule, FDA proposed to weigh the effectiveness criterion more heavily when the bulk drug substance was proposed to treat a serious or life-threatening disease, and to give the safety criterion more weight when the substance was proposed for treatment of a less serious disease. The commenter asserted that there is no rational basis for such a standard.

(Response 7) We disagree with the comment. As we explain in the 2016 proposed rule, when a bulk drug substance is proposed to treat a more serious or life-threatening disease, there may be more serious consequences associated with ineffective therapy. When evaluating a bulk drug substance that is proposed for the treatment of a less serious illness, FDA will generally be more concerned about the safety of the substance than about its effectiveness. For these reasons, we find no reason to discontinue consideration of the seriousness of the condition the bulk drug substance is nominated to treat.

(Comment 8) One comment objected to the process FDA used to implement the criteria, noting that FDA was required to consult with the PCAC and obtain stakeholder input through notice and comment rulemaking before going forward with substance evaluations using the proposed criteria. The commenter asserts that there was no formal debate or discussion of the criteria with the PCAC.

(Response 8) We acknowledge that FDA began considering the proposed criteria and presenting recommendations to the PCAC before the criteria were finalized in this rulemaking. We believe that the criteria could not have been fully vetted and considered, by both the PCAC and USP, as well as commenters to the 2016 proposed rule, without illustration of how those criteria would apply in practice to evaluation of nominated bulk drug substances. As discussed

in this rulemaking, FDA has considered the comments received on the proposed criteria and has found no basis to change those criteria based on the comments received.

We disagree, however, with the comment asserting that there was no formal debate or discussion of the criteria with the PCAC. As discussed in the 2016 proposed rule, FDA presented the criteria to the PCAC and discussed the criteria with the PCAC at its February 23, 2015, meeting (Ref. 2). The public had the opportunity to attend and speak at the PCAC meeting at which these criteria were discussed. The public also had the opportunity to review the transcript of the discussion that took place at the PCAC meeting, both prior to the publication of the proposed rule via publication of the transcript on the FDA website and through the docket for the proposed rule, where the transcript was included as a reference. FDA also consulted with USP regarding the criteria, and USP agreed with the proposed criteria (Refs. 3 and 4).

2. Application of the Proposed Criteria to Date

(Comment 9) Some commenters objected to the proposed criteria as being underinclusive of the factors FDA has been applying in practice in its evaluations of the nominated bulk drug substances. Specifically, several comments stated that FDA's application of the proposed criteria has been skewed by inappropriate consideration of the availability of an investigational new drug (IND) application pathway, which should not be relevant to FDA's recommendation of whether to include a particular bulk drug substance on the 503A Bulks List.

(Response 9) We disagree with the comment that the proposed criteria are underinclusive of the factors FDA has been applying in practice. While the PCAC presentations and discussions have encompassed some information of interest that is not directly related to the four criteria, such as the differences in regulatory standards between dietary supplements and drug products, or general information about compounding facilities, that information was not the basis of FDA's

recommendations or decisions with respect to the bulk drug substances. Rather, in each of FDA's reviews (included in the record for the 2016 proposed rule), our recommendations have been derived directly from consideration and balancing of the four criteria: (1) physical and chemical characterization of the substance; (2) any safety issues raised by the use of the substance in compounded drug products; (3) available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and (4) 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.

The option of making a substance available through an IND application has been discussed by the PCAC and addressed in some reviews to help inform the public of ways in which the drug can be further studied and used to treat patients. In no review to date, however, has the option of pursuing an IND been a basis in FDA's proposals to include, or not to include, a nominated bulk drug substance on the 503A Bulks List. For each substance evaluated to date, FDA has made its proposals based on the four criteria described above, without regard to the existence of, or option to pursue, an IND. We note that FDA can make recommendations to the PCAC, but the Agency cannot control the content of the PCAC's discussions or its advice. FDA takes the PCAC's discussions and advice, including the basis for any advice, into account when considering whether to propose a substance be placed on the 503A Bulks List.

As stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it has inappropriately considered the availability of an IND in any particular case, FDA will

consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 10) One comment asserted that FDA's application of criteria to evaluate bulk drug substances to date has been inconsistent. For example, according to the commenter, in some cases FDA and the PCAC recommended to include a bulk drug substance on the 503A Bulks List so there is an alternative to approved products, but in other cases, FDA and the PCAC recommended to not include a substance on the list because there is already an approved product available.

(Response 10) We disagree with this comment. As we noted above, the criteria are applied on a substance-by-substance basis, and a criterion that may be weighed heavily for one bulk drug substance might be weighed differently for another, given the risks and benefits that may be presented by a particular substance. We have applied, and will continue to apply, the criteria consistently, weighing them as appropriate based on the nature of the substance and proposed use, among other things. Also as stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP and is the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it has not applied the criteria correctly in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 11) One comment objected to the level of evidence of clinical effectiveness and toxicology FDA has been considering in its application of the proposed criteria. According to the comment, these high standards of evidence are unreasonable and change fundamental

standards of practice. The comment asserts that FDA appears to be requiring studies that can survive any criticism and is ignoring the role of physician decisions based on clinical experience.

(Response 11) We disagree with the comment. As stated in the 2016 proposed rule, FDA recognizes that it is unlikely that candidates for the 503A Bulks List will have been thoroughly investigated in in vitro or in animal toxicology studies, or that there will be well-controlled clinical trials to substantiate their safe use in humans. We note that the evidence that has supported FDA's recommendations to place particular substances on the 503A Bulks List to date has not been of the type or quality that is ordinarily required and evaluated as part of the drug approval process. We further note that we considered the input of physicians and their clinical experience to the extent that information is provided to the Agency, including that provided during PCAC meetings. We find no reason to reduce the amount of evidence FDA has considered necessary to support a recommendation to include a bulk drug substance on the 503A Bulks List and believe that doing so would not be in the interest of public health.

(Comment 12) One comment asserted that application of the criteria to date has been too narrow in its application to a particular proposed use.

(Response 12) We disagree and believe that it is necessary to evaluate a nominated bulk drug substance in the context of the uses proposed for compounded drug products that include the substance. We acknowledge that inclusion of a substance on the 503A Bulks List is not limited to a specific use. However, for evaluation purposes, FDA finds it necessary to consider the criteria, particularly the effectiveness criterion, in the context of a specific proposed use or uses. Given the number of substances nominated for inclusion on the list, it would not be possible for FDA to consider all possible uses for a compounded drug product that includes the nominated substance. Therefore, we find it reasonable to rely on information from the interested

parties who nominated the bulk drug substances to identify the proposed uses, and for FDA to evaluate the substance in the context of those uses.

Nevertheless, as indicated in the 2016 proposed rule, when FDA is aware of another use that may be relevant to its evaluation of a substance for the 503A Bulks List, such as when a use other than that for which it was nominated is widespread, FDA may consider that use in its discretion.

As discussed in the 2016 proposed rule, FDA has opened a docket through which interested individuals may nominate additional bulk drug substances or provide additional information about substances already nominated with sufficient information for the 503A Bulks List (see Docket No. FDA-2015-N-3534). If an interested party believes that the nominations for a particular substance did not include a proposed use that it would like to be reviewed, and that substance has not yet been addressed in an NPRM, additional information or nominations may be provided through that docket.

(Comment 13) One comment asserted that application of the criteria to date has given undue weight to possible side effects or safety concerns related to use of compounded drug products, which are often speculative.

(Response 13) We disagree with the comment. FDA's reviews of nominated substances to date have appropriately balanced the safety criterion with the other three criteria, and FDA has applied its scientific judgment to identify side effects or safety concerns based on available data and information. As stated above, FDA's application of the criteria to particular bulk drug substances is subject to discussion with the PCAC and USP, and is also the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes it has inappropriately considered safety information related to compounded drug

products in any particular case, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 14) One comment objected to statements made during PCAC meetings indicating concern that, if a bulk drug substance is placed on the list, drug products compounded with that substance could be marketed with any claims. The comment notes that marketing a drug product for unsubstantiated claims is illegal, and if FDA and PCAC are concerned that this is happening, appropriate action and education should be undertaken. The commenter asserts that the possibility of misleading marketing should not be considered when determining whether to include a bulk drug substance on the 503A Bulks List.

(Response 14) We did not consider the possibility of misleading marketing when determining whether to include a bulk drug substance on the 503A Bulks List. Under section 502(bb) of the FD&C Act, a compounded drug will be deemed misbranded if the advertising or promotion of such compounded drug is “false or misleading in any particular.” In addition, under section 502(a) of the FD&C Act, a drug will be deemed misbranded if its labeling is “false or misleading in any particular.” However, the existence of false or misleading advertising is not one of the four criteria considered when evaluating a nominated substance for inclusion on the 503A Bulks List.

3. FDA’s Proposals on Specific Substances

(Comment 15) One comment requests that the listing of NAG codified at § 216.23(a) (21 CFR 216.23(a)) not be limited to topical use only, and instead, to allow use of that substance by any route of administration. The comment notes that one of the nominations for that bulk drug substance was not limited to topical use.

(Response 15) We disagree that the listing for NAG in the codified should be expanded beyond topical use. As we explained in the *Federal Register* of July 2, 2014 (79 FR 37747 at 37748 (July 2014 Request for Nominations)), which detailed the type of information to be provided with nominations, FDA only intended to review nominations that were supported with adequate data and information. Doing so has allowed FDA to focus its limited resources on the nominated uses and routes of administration for which nominators have provided the most support. Also, as indicated in the July 2014 Request for Nominations, the Agency reviewed information for multiple nominations of the same substance collectively (79 FR 37747 at 37749).

None of the nominations for NAG proposed or provided information that would support administration of NAG by any route of administration other than topical. The nomination from the International Academy of Compounding Pharmacists mentioned in the comment did not specify a proposed use or route of administration. Rather, the nomination stated only that “[t]he very nature of a compounded preparation for an individual patient prescription as provided for within FDCA 503A means that the purpose for which it is prescribed is determined by the health professional authorized to issue that prescription.” (Ref. 5.) Taken alone, this nomination did not provide adequate support to allow FDA to evaluate the nominated substance (for topical or other routes of administration), and it was only considered collectively with the other nominations for NAG for topical use. As noted in the 2016 proposed rule, individuals and organizations may petition FDA under 21 CFR 10.30 to amend the list, including to request that the Agency evaluate NAG for routes of administration other than topical. See Response 31 for further discussion of the petition process.

(Comment 16) Some comments object to the exclusion of oxitriptan from the 503A Bulks List and request that oxitriptan be included on the list codified at § 216.23(a). The comments

state that oxitriptan is widely sold as a dietary supplement and that it has an extensive safety record through its long history of use as a dietary supplement, which they believe should be given more weight. The comments assert that patients benefit from a relationship with their prescriber and pharmacist that is not available in the dietary supplement context because dietary supplements are purchased over the counter. According to one of the commenters, there is no evidence of any risk that oxitriptan would have the same side effects as other medications used to treat depression, and the mechanism of action of oxitriptan is demonstrably different from that of approved therapies. The comment asserts that oxitriptan's safety profile is significantly better than that of approved products. One comment also asserts that oxitriptan has been shown to be effective in the treatment of a variety of conditions, including depression and insomnia.

(Response 16) We have considered the comments and the references cited therein (Refs. 6 to 9), and find no reasoning or data that cause FDA to change its evaluation not to include this substance on the 503A Bulks List. As noted above, the availability of a substance as a dietary supplement is not a criterion considered when evaluating a substance for inclusion on the 503A Bulks List. Dietary supplements are intended for oral ingestion only, are not intended to be used to treat diseases, and therefore, are subject to a different legal and regulatory scheme than drug products. Section 503A addresses compounded drug products only. We acknowledge that FDA's reviews and PCAC meetings included discussions about the availability of dietary supplements with dietary ingredients that were the same or similar to the nominated bulk drug substances. As noted in prior PCAC discussions, FDA's proposals in this context do not impact a substance's availability as a dietary supplement.

Regarding the argument that there is no evidence of any risk that oxitriptan (also known as 5-hydroxytryptophan or 5-HTP) would have the same side effects as other medications used to

treat depression, as previously stated in FDA's review (Ref. 5), there is a dearth of reliable scientific data regarding the safety of oxitriptan. We found no data indicating that the use of oxitriptan for depression would be free of the same side effects as other medications used to treat depression, and no reliable scientific data were provided in the comments received on the proposed rule to support this assertion.

Regarding the argument that the mechanism of action of oxitriptan is demonstrably different from that of approved therapies, as previously stated in FDA's review, the psychoactive action of oxitriptan is related to increased production of serotonin in central nervous system tissue (id). Based on this mechanism of action, oxitriptan, particularly with concomitant use of antidepressant drug products, could result in serotonin syndrome, a life-threatening drug interaction, and cases that are likely to be serotonin syndrome have been reported with the use of oxitriptan as a dietary supplement (Ref. 10). In fact, one source cited by a commenter warns against taking oxitriptan with certain approved antidepressants because both increase the brain chemical serotonin and taking both "might increase serotonin too much and cause serious side effects including heart problems, shivering, and anxiety" (Ref. 7).

Regarding the argument that oxitriptan's safety profile is significantly better than that of approved products, we disagree. As explained in Response 5, data comparing the safety profiles of compounded drug products with approved drug products are generally not available, and we do not have any such comparative data here. As stated above, the absence of information does not mean that safety risks do not exist. In contrast, approved drug products have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the benefits of the drug product for the approved conditions of use have been found to outweigh the risks.

Regarding the argument that oxitriptan has been shown to be effective for the treatment of a number of conditions, including depression and insomnia, similarly, the comments provided no reliable scientific data that would cause FDA to change its evaluation of oxitriptan, which balanced the available data on effectiveness with the other three criteria. As stated in the 2016 proposed rule, data supporting the drug's effectiveness for depression and insomnia are limited, and there are no data to support the effectiveness of the long-term use of oxitriptan to treat depression. FDA's conclusion in the 2016 proposed rule regarding the effectiveness of oxitriptan for insomnia and depression was based on FDA's consideration of more recent and comprehensive data than that provided by the commenters, and the information provided by the commenters does not alter that conclusion. We also note that one source cited by a commenter stated that there is insufficient evidence to rate the effectiveness of oxitriptan for insomnia (Ref. 7).

In sum, we have reviewed the scientific references and considered the reasoning set forth in the comments, and they do not change FDA's analysis of oxitriptan as stated in our review (Ref. 5) or our conclusion that it should not appear on the 503A Bulks List.

(Comment 17) Some comments object to the exclusion of piracetam from the 503A Bulks List and request that piracetam be included on the list codified at § 216.23(a). The comments note that FDA has recognized that there is not a significant safety risk related to the use of piracetam. They assert that the recommendation to exclude piracetam from the 503A Bulks List was based on a presumption that piracetam could be obtained through an IND, which was not a proper consideration. One comment provided data about the effectiveness of piracetam for short-term cognitive performance (Ref. 11) and the safety of its administration in high doses to patients with acute stroke (Ref. 12).

(Response 17) We have considered the comments and references cited therein and find no reasoning or data that cause FDA to change its evaluation not to include this substance on the 503A Bulks List. Regarding the safety of piracetam, we note that while our review of piracetam indicated that doses of less than 8 grams per day² appear to be unlikely to cause serious adverse reactions or drug interactions, the review also described safety concerns associated with certain patient populations and certain concomitant medications (Ref. 13). Piracetam is not recommended for patients with severe renal impairment because clearance of the compound is dependent on the renal creatinine clearance and would be expected to diminish with renal insufficiency. Piracetam is also not recommended for those taking concomitant anticoagulants because piracetam reduces platelet function, interferes with clotting factors, and prolongs bleeding time at certain doses. We also note that, in evaluating piracetam, we considered the three other criteria in addition to the safety of piracetam.

Although it is well characterized chemically and physically and has been used in compounded drug products for approximately 40 years, as stated in its review, FDA is concerned about the effectiveness of piracetam (id.). The available data do not show a clear benefit associated with the use of piracetam (id.). Numerous studies of piracetam have been conducted, and all but a few were designed poorly or used inappropriate statistical methods to support conclusions that piracetam is effective as a treatment for the studied condition (id.). The publications that suggest piracetam is effective for treating cognitive impairment, acute vertigo, or stroke are inconsistent, and there are also publications that conclude that piracetam is ineffective for treating these same conditions (id.). We were able to identify a single, well-

² Note that FDA's review stated that doses of less than "8 kg/day" appear unlikely to cause serious adverse reactions or drug interactions, but "kg" was a typographical error. That statement of the review should have been "8 g/day."

designed and executed study of piracetam, which showed that it is ineffective for the treatment of cognitive impairment (Ref. 14).

The two scientific articles referenced in the comments, one of which is discussed in FDA's evaluation of piracetam (Ref. 11), and the other of which addressed the safety of high doses of piracetam when used as a treatment for acute stroke (Ref. 12), do not address FDA's concerns regarding the lack of data supporting its effectiveness in treating serious and life-threatening conditions such as stroke. For the reasons set forth above, neither the scientific references nor the reasoning set forth in the comments provide a basis for FDA to change its analysis of piracetam according to the four criteria (Ref. 13), or FDA's ultimate conclusion that piracetam should not appear on the 503A Bulks List.

Finally, we acknowledge that the possibility of pursuing an IND application for piracetam was discussed at the PCAC meeting (Ref. 15) to inform the public of a pathway to study and access piracetam. FDA did not consider the availability of an IND in its review of piracetam under the four criteria, however (Ref. 13). As FDA explained in its review, based on the absence of a clear benefit associated with piracetam, the seriousness of the conditions for which piracetam was proposed for use, and the availability of safe and effective medications for many of these uses that have undergone greater scientific scrutiny (*id.*), FDA proposed piracetam not be placed on the 503A Bulks List.

(Comment 18) One comment objects to the exclusion of silver protein mild from the 503A Bulks List and requests that silver protein mild be included on the list codified at § 216.23(a). The comment states that silver protein mild is well characterized physically and chemically, has a long history of use, is relatively nontoxic, and side effects are only rarely reported.

(Response 18) We have considered the comment and find no reasoning or data therein that cause FDA to change its evaluation not to include this substance on the 503A Bulks List. As stated in the 2016 proposed rule, silver protein mild is not well-characterized, and the term “silver protein mild” can refer to a variety of different drug products. FDA is also concerned about the safety of silver protein mild, which can cause argyria (a permanent ashen-gray discoloration of the skin, conjunctiva, and internal organs) (Ref. 13). Despite the commenter’s characterization of the substance as relatively nontoxic, FDA remains concerned that chronic use of silver protein mild may result in permanent discoloration of the conjunctiva, cornea, and/or lens (*id.*). As for the commenter’s characterization that the side effects are rarely reported, we note that the use of silver protein mild declined precipitously after the introduction of FDA-approved ocular anti-infectives. As described in FDA’s review, numerous articles and books published when silver protein mild was more commonly used described deposits of silver in the conjunctiva, lacrimal sac, cornea, and lens following administration (*id.*).

We also note that there is no reliable evidence that silver protein mild would be effective for the proposed use. It has been studied in two controlled studies. In one study, silver protein mild was found to be numerically, although not statistically, inferior to having no treatment at all. In the second study, silver protein mild was found to be inferior to povidone iodine, which is an FDA-approved drug product (*id.*). While silver protein mild does have a long history of use, dating back to the early 1900s, as noted above, the use of silver protein mild declined dramatically after the introduction of FDA-approved ocular anti-infectives (*id.*).

The reasoning set forth in the comment does not address FDA’s concerns about the characterization, safety, or effectiveness of silver protein mild, and does not change FDA’s conclusion that silver protein mild should not appear on the 503A Bulks List.

(Comment 19) Some comments object to the exclusion of tranilast from the 503A Bulks List and request that tranilast be included on the codified list at § 216.23(a). The commenters note that FDA's proposal not to include tranilast is contrary to the advice of the PCAC. They assert that FDA's view is based on a faulty understanding of the increased bilirubin observed in clinical trials and note that the proposed topical dosage is well below that used in those trials. One comment described anecdotal reports that the topical use of tranilast has been effective in the treatment of keloids and hypertrophic scars. Another comment asserted that tranilast has been available in Japan for over 30 years, apparently without detrimental effects.

(Response 19) We have considered the comments and decline to include tranilast on the 503A Bulks List. As stated in the 2016 proposed rule, FDA has serious concerns about the safety of tranilast when administered orally, and there is insufficient information about the systemic absorption of topical tranilast formulations to determine whether topical administration of the drug product presents the same safety concerns (81 FR 91071 at 91079). No new data about the use of tranilast were provided in the comments; rather, the comments provided only anecdotal reports about the use of tranilast and further discussion of the same data presented to the PCAC, which FDA considered prior to publishing the 2016 proposed rule. The reasoning in the comments did not sufficiently address FDA's safety concerns regarding the use of this substance.

We acknowledge that the PCAC recommended including tranilast on the 503A Bulks List with a restriction to topical use. However, advisory committee recommendations are not binding on FDA. Rather, FDA considers the PCAC's advice but makes an independent judgment regarding whether particular substances should appear on the 503A Bulks List. As we explained in our supplemental review of tranilast (Ref. 16) and the 2016 proposed rule, the government-

approved Japanese tranilast product label provided evidence of teratogenicity in animals and contraindicated the use of tranilast in pregnant women or women who may become pregnant. We did not find that the risk of prescribing a potential teratogen to women who may be or may become pregnant was outweighed by the potential benefit of treating scar tissue. Therefore, FDA continues to believe that the criteria weigh against placing tranilast on the 503A Bulks List.

Regarding the commenter's statements about the effectiveness of tranilast for keloids and hypertrophic scarring, scientific data supporting effectiveness for those uses are lacking. While there is some evidence that tranilast may be effective for allergic disorders, evidence of effectiveness for those other uses is either not available or inconclusive (Refs. 5 and 16).

(Comment 20) One comment objected to the rejection of substances that are dietary supplements from the 503A Bulks List. The commenter states that by rejecting these substances from the list, FDA is forcing consumers to use products that are subject to less quality oversight and lack physician supervision. The commenter proposes that dietary supplements only be rejected for proven safety concerns.

(Response 20) As stated in Response 16, a substance's availability as a dietary ingredient or supplement is not a criterion when evaluating a substance for inclusion on the 503A Bulks List. Dietary supplements are intended for oral ingestion only, and are not intended to be used to treat diseases, and therefore, are subject to a different legal and regulatory scheme than drug products. Section 503A of the FD&C Act addresses compounded drug products only. To the extent FDA's reviews and PCAC meetings included discussions about the availability of dietary supplements with dietary ingredients that were the same or similar to the nominated bulk drug substances, we note that FDA's proposals in this context do not impact a substance's availability as a dietary supplement.

Regarding the comment about the lack of quality oversight for dietary supplements, we note that dietary supplement manufacturers are required to comply with FDA's Current Good Manufacturing Practice regulations for dietary substances and are subject to inspection by FDA (21 CFR part 111). Regarding physician supervision, we note that physicians may recommend dietary supplements to their patients regardless of whether the substance appears on the 503A Bulks List.

4. Dietary Supplement Monographs and Other Monographs

(Comment 21) Some commenters objected to FDA's interpretation, as stated in the 2016 proposed rule, that dietary supplement monographs are not "applicable monographs" for purposes of determining which substances may be included in compounded drug products under section 503A(b)(1)(A)(i)(I) of the FD&C Act. They note that physicians may prescribe dietary supplements. They also state that in a "2014 guidance,"³ FDA said that dietary supplement monographs were "applicable monographs" under section 503A, and that change in policy has not been explained.

(Response 21) We disagree that dietary supplement monographs should be considered "applicable monographs" for purposes of section 503A of the FD&C Act. As stated in the 2016 proposed rule, section 503A sets forth conditions that must be met for a compounded drug product to qualify for certain exemptions from the FD&C Act. Among other conditions, section 503A(b)(1)(A)(i) of the FD&C Act requires that a bulk drug substance used in a compounded drug product meet one of the following criteria: (1) comply with the standards of an applicable USP or NF monograph, if one exists; (2) be a component of an FDA-approved human drug product, if a monograph does not exist; or (3) be on a list of bulk drug substances that may be

³ One comment appears to refer to the July 2014 Request for Nominations as "guidance" on this topic.

used for compounding, to be developed by FDA through regulation. FDA has interpreted the term “an applicable United States Pharmacopoeia (USP) or National Formulary (NF) monograph” to refer to official drug substance monographs. Therefore, a substance that is the subject of a dietary supplement monograph, but not a drug substance monograph, may only be compounded if the substance is a component of an FDA-approved drug product or is on the FDA’s list of bulk drug substances that may be used for compounding.

This interpretation is both legally supportable and in the best interest of the public health. Under the FD&C Act, drugs and dietary supplements are different product categories that are subject to different regulatory schemes. Section 503A, the key statutory provision for this rulemaking, concerns pharmacy compounding of drug products, not dietary supplements. It states that a drug product may be compounded under section 503A(a) of the FD&C Act if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that comply with the standards of an *applicable United States Pharmacopoeia or National Formulary monograph*, if a monograph exists, and the United States Pharmacopoeia chapter on pharmacy compounding (emphasis added). (See section 503A(b)(1) of the FD&C Act.)

Accordingly, it is reasonable to interpret the phrase “applicable United States Pharmacopoeia monograph” in this statutory provision as a reference to USP *drug* monographs, not USP dietary supplement monographs. Moreover, adopting the alternative interpretation urged by the comment--i.e., that “applicable” USP monographs include dietary supplement USP monographs--would not be in the best interest of the public health. USP monographs for dietary supplements can differ in significant ways from USP monographs for drugs because of the differences between dietary supplements and drug products. For example, dietary supplements

are intended for ingestion only, and the standards contained in the USP dietary supplement monographs are likewise intended for dietary supplements that will be ingested; the standards are not appropriate for use in compounding drug products that may have different routes of administration (e.g., intravenous, intramuscular, topical). In addition, the USP limits for elemental impurities are different for drugs and dietary supplements: there are limits specified in USP General Chapters for many more elemental contaminants for drugs than there are for dietary supplements. Furthermore, the bioburden allowable for dietary supplements is considerably higher than that allowed for drug substances. Relying on the standards of a dietary supplement monograph for a substance that will be used in compounding drug products could therefore put patients at risk.

We disagree with the commenter's statement that a 2014 guidance stated that dietary supplement monographs were "applicable monographs" under section 503A of the FD&C Act. FDA is unaware of any Agency statements that support that view, including the July 2014 Request for Nominations.

(Comment 22) One comment asserted that the Homeopathic Pharmacopeia of the United States (HPUS) homeopathic monographs and other types of monographs should be considered "applicable monographs" under section 503A(b)(1)(A)(i)(I) of the FD&C Act, making substances that are the subject of such monographs eligible for use in compounding. The comment asserted that the Drug Quality and Security Act (DQSA) (Pub. L. 113-54) gives FDA authority to designate sources other than USP or NF monographs as "applicable monographs." The comment also noted that the FD&C Act recognizes the HPUS as "official" in 21 U.S.C. 358(b), and in the definitions at 21 U.S.C. 321, the FD&C Act defines "drug" to include articles recognized in the HPUS.

(Response 22) We disagree that HPUS homeopathic monographs and other types of monographs should be considered “applicable monographs” under section 503A. The provisions of DQSA cited in the comment do not apply to section 503A of the FD&C Act. Rather, the language of section 503A explicitly applies only to applicable USP or NF monographs. Therefore, we decline to consider HPUS or other types of monographs to be “applicable monographs” under section 503A(b)(1)(A)(i)(I) of the FD&C Act.

(Comment 23) One commenter asserted that incorporating the statements about FDA’s interpretation of “applicable monographs” from the Interim Policy Guidance effectively and improperly converts that guidance document to rulemaking. The commenter pointed out that regulations cannot be issued through guidance documents and stated that the guidance should be rescinded.

(Response 23) We disagree with this comment. Describing an interpretation of the applicable statute in both a guidance document and in a preamble to a proposed rule does not “convert” the guidance document to a rulemaking and has no impact on the status of the guidance. The guidance document was issued in accordance with our “Good guidance practices” regulation (21 CFR 10.115).

5. Conflict of Interest

(Comment 24) One comment stated that FDA should consider its “conflict of interest” arising from the Agency’s receipt of funds under the Prescription Drug User Fee Act (PDUFA) related to new drug applications (NDAs). According to the commenter, these funds cause FDA to be biased in favor of approved products.

(Response 24) We disagree with this comment. It is unclear what action the commenter was suggesting that FDA take to address this perceived “conflict of interest.” We note that the

receipt of PDUFA fees related to NDAs has not affected FDA's ability to be impartial when evaluating bulk drug substances for inclusion on the 503A Bulks List. The Agency believes that compounded drugs can play a critical role for patients whose medical needs cannot be met by an approved drug.

Moreover, FDA's recommendations on particular bulk drug substances are subject to discussion with the PCAC and USP, and are the subject of notice and comment rulemaking. If, through the rulemaking process, FDA receives feedback that any party believes its recommendations are biased in any particular cases, FDA will consider that feedback before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

6. Qualifiers for Use of Substances on the 503A Bulks List

(Comment 25) One comment requested that FDA allow inclusion of bulk drug substances on the list with certain qualifiers or limited uses, such as dose or dosage form. The comment stated that such qualifiers will give FDA greater leeway to add bulk drug substances to the list, which will benefit patients.

(Response 25) We agree that in some limited cases, it may be appropriate to place bulk drug substances on the 503A Bulks List subject to a restriction on use, such as the route of administration. For example, several of the substances that are being added to the list in this rulemaking are restricted to topical use only. For the substances we are not including on the list in this rulemaking, we found no relevant qualifiers on the compounded drug product, such as route of administration, that would have justified inclusion of the substances on the list.

7. Process Issues Related to FDA's Evaluation of Nominated Bulk Drug Substances and PCAC Consultations

(Comment 26) One comment raised concerns about the composition of the PCAC. The commenter asserted that the professions most familiar with compounded drug products are not represented on the PCAC, and neither FDA nor the PCAC has the necessary expertise to make judgments on the nominated bulk drug substances. In particular, according to the commenter, naturopaths need to be consulted, and a counterbalance to the representation by Public Citizen and the Pew Charitable Trusts is needed on the committee. The comment stated that PCAC members may have conflicts of interest.

(Response 26) We disagree with the comment. Of the current PCAC members, seven are pharmacists, and five are physicians. Twelve committee members have experience related to drug compounding, including experience in the preparation, prescribing, and use of compounded medications, as well as compounding-related research activities. In accordance with section 503A of the FD&C Act, one member is a representative from USP, and one member is a representative from the National Association of Boards of Pharmacy.

Industry participated in the selection of two additional committee members--one from the pharmaceutical manufacturing industry and one from the compounding industry. Additionally, a consortium of consumer advocacy representatives participated in the selection of a consumer representative.

More than 100 names were submitted to the Agency in response to the January 13, 2014, *Federal Register* notices requesting nominations.⁴ (79 FR 2177; 79 FR 2178; 79 FR 2179.) In addition, FDA identified qualified candidates from its own pool of special government

⁴ FDA issued another request for nominations for the PCAC in the *Federal Register* of March 27, 2018 (83 FR 13133).

employees. The selection process of candidates that were not designated representatives of particular groups included evaluation for conflicts of interest as required by 21 CFR 14.80, and for the relevancy of their qualifications for the purpose of the committee. Candidates with actual or potential conflicts of interest in matters that would come before the committee were eliminated from consideration. For example, for those candidates not representing a particular group, FDA reviewed whether the candidate owned a compounding pharmacy, consulted for the compounding industry, or supplied bulk drug substances for compounding, because those activities would likely raise a financial interest that could be affected by the matters expected to come before the committee.

In general, members are invited to serve for overlapping terms of up to 4 years. As it has to date, the Agency will consider future nominations for membership and strive to select members with robust and relevant experience and expertise related to drug compounding.

Nominations may be submitted to the Advisory Committee Membership Portal at any time and submitted nominations will be considered as vacancies occur. See <https://www.accessdata.fda.gov/scripts/FACTRSPortal/FACTRS/index.cfm>. See <https://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/ApplyingforMembership/default.htm> for more information on the nomination procedure.

(Comment 27) One comment asserted that FDA has “unfairly screen[ed]” the evidence provided by nominators to the PCAC, has “misrepresented” the availability of other routes of approval of drug products compounded with the nominated bulk drug substance, and has “manipulated” the PCAC into rejecting certain nominated substances. The commenter stated that FDA appeared to be “cherry-picking” studies only to show negative data, and was not

scrutinizing studies that showed safety concerns with the use of the bulk drug substance in the same way that it has scrutinized studies the nominators put forward to show effectiveness.

(Response 27) We disagree with this comment. As stated above, FDA is determining whether to place a substance on the list after weighing available data and information in light of the four criteria set forth in this rulemaking and considering feedback from PCAC, USP, and the public. FDA considers publicly available studies that are relevant to the evaluation criteria, regardless of the source of those studies.

As stated above, if members of the public believe FDA is not giving adequate weight to certain studies, or is otherwise misrepresenting information presented to the PCAC in any particular case, they are encouraged to submit a comment to the docket for the NPRM in which the substance at issue is addressed. Nominators and the public are also invited to present at PCAC meetings where they have an opportunity to discuss their interpretation of the relevant studies and address the PCAC regarding each substance considered. FDA will consider all feedback received before finalizing its proposal to include, or not include, a substance on the 503A Bulks List.

(Comment 28) Some comments stated that nominators were not being given equal time with FDA to make presentations to the PCAC, and instead were limited to 10-minute presentations. Commenters asserted that this imbalance is unfair and has resulted in skewed decision making by the PCAC. Commenters also asserted that nominators were given insufficient notice of PCAC meetings and did not have adequate time to prepare.

(Response 28) We acknowledge that FDA presentations have been allotted more time than those by nominators, which we believe is appropriate given that FDA is tasked with

developing the 503A Bulks List and is necessary for FDA to present fully on the reviews of the bulk drug substances.

Regarding notice of PCAC meetings, FDA has notified the public at least 20 days prior to PCAC meetings, and the Agency strives to give notice further in advance where possible. However, further advance notice is not always possible due to the need to coordinate various logistical issues.

(Comment 29) Some commenters noted that it was not possible for nominators to provide the information FDA requested in its July 2014 Request for Nominations for the list of bulk drug substances that can be compounded under section 503A of the FD&C Act for two reasons. First, commenters stated there is a gap between the stated criteria and how FDA is applying the criteria, and therefore, nominators did not have sufficient notice of what information would be needed for FDA's decision making. Second, commenters asserted that it is not possible to provide the information FDA required for a nomination because decisions about how a compounded drug is used are at the discretion of the physician.

(Response 29) We disagree with this comment. As noted previously, FDA is applying the four criteria set forth in this rulemaking when evaluating bulk drug substances for inclusion on the list. FDA considers the information requested in the July 2014 Request for Nominations and bases its decision on the physical and chemical characterization, safety, effectiveness, and historical use of the bulk drug substance in compounded drug products. If nominators believe that there is additional information relevant to those four criteria that would be helpful to consideration of nominations that are still pending with FDA for evaluation, that information can be submitted for FDA's consideration via Docket No. FDA-2015-N-3534.

With respect to the concern about challenges in submitting nominations because physicians may prescribe compounded drug products tailored to the needs of individual patients, we note that physicians and prescribers, who may have unique insights on how compounded drug products are used in particular cases, may submit information for FDA's consideration via Docket No. FDA-2015-N-3534.

(Comment 30) Some comments objected to FDA's process regarding bulk drug substances that were nominated without adequate information for FDA to evaluate the substance. One commenter requested that FDA issue letters to the parties whose nominations were rejected informing them of the specific deficiencies with the nomination. The comment described this process as resource-intensive, but necessary because access to the bulk drug substance is being "cut off."

(Response 30) We disagree with this comment. The July 2014 Request for Nominations identifies the information that the Agency is requesting in the nominations, and nominations containing the information requested in the July 2014 Request for Nominations will be deemed adequate.

As described in the Interim Policy Guidance, Docket No. FDA-2015-N-3534 is open to receive new nominations, including renominations of substances previously nominated with inadequate supporting information, or additional information about bulk drug substances previously nominated with adequate information to allow evaluation. FDA is evaluating new information provided to the docket on a rolling basis and is periodically adding newly nominated or renominated substances to "Category 1" (the category for adequately supported nominations that will be evaluated for inclusion on the 503A Bulks List) when appropriate.

(Comment 31) One comment stated that clarity is needed regarding the process by which substances that have been “considered and rejected” by the PCAC may be renominated. The comment noted that new or additional information about the substance may become available that warrants further evaluation by FDA and the PCAC.

(Response 31) We have considered this comment and are clarifying the process for providing additional information about substances that have been considered by the PCAC. Bulk drug substances, including those that have been evaluated by FDA and presented to the PCAC and USP, remain under consideration until they are addressed in a final rule. Individuals and organizations may submit additional information relevant to the evaluation criteria about a use proposed in the original nomination(s) for a bulk drug substance to Docket No. FDA-2015-N-3534 until that substance is addressed in an NPRM. When a substance is addressed in an NPRM, individuals and organizations may submit additional information relevant to the evaluation criteria about the use(s) evaluated for that bulk drug substance as a comment to that proposed rule. As noted above, after the substance is addressed in a final rule, individuals and organizations may submit a citizen petition to FDA under 21 CFR 10.30 asking FDA to amend the list (i.e., to add or delete bulk drug substances).

If an individual or organization seeks to use a bulk drug substance that has been evaluated by FDA and not recommended in FDA’s review for placement on the 503A Bulks List, for a use, dosage form, or route of administration that was not previously evaluated by FDA, or where there is otherwise a substantive change between the use of the bulk drug substance sought by the individual or organization and how it was evaluated by FDA, the individual or organization may file a citizen petition under 21 CFR 10.30 requesting that FDA reconsider its evaluation of the bulk drug substance, regardless of whether that substance has

been addressed in an NPRM or final rule. In responding to such citizen petitions, FDA generally intends to consider whether, for example, the petitioner provides information not previously considered or shows a significant change in circumstances supported by scientific references that alters the Agency's analysis of the four criteria.

(Comment 32) One comment stated that FDA is only sending certain nominations to the committee and appeared to be "approving" some nominations without consulting the PCAC.

(Response 32) We disagree with this comment, the basis of which is unclear. FDA acknowledges that it is evaluating and consulting with USP and the PCAC only on substances that were nominated with adequate support to allow the Agency's review, as described in the Interim Policy Guidance. FDA is not, however, "approving" the use of any bulk drug substances or proposing to include bulk drug substances on the 503A Bulks List, without consulting USP and the PCAC.

(Comment 33) One comment stated that FDA should have consulted with the PCAC before seeking nominations for the 503A Bulks List or before the Agency evaluated the first set of bulk drug substances for inclusion on the list.

(Response 33) The statute does not require that FDA seek nominations for the 503A Bulks List, or that it consult the PCAC, at any specific stage prior to undertaking rulemaking. Section 503A requires only that FDA consult with the PCAC before issuing regulations to implement subsection (b)(1)(A)(i)(III). FDA sought nominations for the 503A Bulks List and began evaluating substances for inclusion on the list before consulting with the PCAC because this enabled the Agency to prepare robust background materials for PCAC meetings and thereby obtain more meaningful PCAC and public input prior to proposing a rule describing the criteria.

8. Availability of Ingredients for Physician Use

(Comment 34) One comment objected to the rulemaking generally as infringing on the practice of medicine and overregulating physicians' choices of ingredients that can be used in compounded drug products.

(Response 34) The FD&C Act establishes the framework for regulating the drugs that physicians may prescribe. Within this framework, once a drug becomes legally available, with certain limited exceptions, FDA does not interfere with physicians' decisions to use it when they determine that in their judgment it is medically appropriate for their patients. The Agency believes that this rulemaking is consistent with this framework and does not overregulate.

(Comment 35) The comment asserted that this action amounts to poor public health policy and will stifle innovation, because drugs will not be researched or considered for new drug applications unless they show some initial promise.

(Response 35) We disagree. FDA is carrying out its statutory mandate in a manner that seeks to protect the public from exposure to bulk drug substances that are not suitable for use in compounded drug products. We believe it protects the public health to prevent the use of drug products for which there is insufficient evidence that benefits to the patients might outweigh possible risks. To protect human subjects and the integrity of any research, it is important that drugs generally not be studied in humans outside of an investigational new drug application.

9. "Grandfathering In" Use of Bulk Drug Substances

(Comment 36) One comment objected to this rulemaking generally, based on FDA's lack of regulation in this arena previously. The commenter asserted that the compounding industry has developed under State law, and use of bulk drug substances in compounding should be

considered “grandfathered in.” The comment noted that many of the bulk drug substances at issue were in use prior to 1962.

(Response 36) We disagree with this comment. Section 503A of the FD&C Act does not provide for “grandfathering in” the use of bulk drug substances, including those in use prior to 1962. Moreover, FDA is considering the length and extent of the historical use of the bulk drug substance in compounded drug products when determining whether to recommend the substance for inclusion on the 503A Bulks List.

10. “Regulatory Freeze Pending Review” Memorandum and Executive Order 13771

(Comment 37) One comment objected to this rulemaking based on the January 20, 2017, memorandum signed by Reince Priebus on behalf of President Trump entitled “Regulatory Freeze Pending Review” and January 30, 2017, Executive Order 13771 entitled “Presidential Executive Order on Reducing Regulation and Controlling Regulatory Costs” because FDA has not identified two regulations to be eliminated.

(Response 37) The requirements outlined in Executive Orders 13771 and 13777 have been considered in issuing this final rule, and this rule will be accounted for as appropriate under both executive orders.

11. Rulemaking

(Comment 38) Some commenters alleged that FDA’s actions related to this rulemaking, many of which are described in the comments summarized above, have been arbitrary and capricious in violation of the Administrative Procedure Act (APA) (5 U.S.C. 551 *et seq.*). In addition, one commenter stated that FDA’s actions through this rulemaking are arbitrary and capricious because the rulemaking goes beyond concerns about the safety of compounded drug

products, which applies only to sterile drug products. That commenter noted that Congress enacted the DQSA to address concerns surrounding sterility and contamination.

(Response 38) We disagree with this comment. FDA has followed proper rulemaking procedures and has not acted in an arbitrary and capricious manner in violation of the APA.

Section 503A requires FDA to issue the 503A Bulks List through a rulemaking process, and it gives the Agency discretion to consider relevant criteria (see section 503A(c)(2) of the FD&C Act). FDA is establishing the four criteria described above, and applying these criteria to bulk drug substances that are not the subject of an applicable USP-NF monograph or a component of an FDA-approved drug product. Such substances may be used to compound sterile or non-sterile drug products. Accordingly, FDA applies the established criteria to bulk drug substances that may be used to compound sterile or non-sterile drug products. FDA notes that the safety criterion is not limited to consideration of sterility and contamination, and FDA may have safety concerns about bulk drug substances used to compound sterile and non-sterile drug products.

VI. Effective Date

This final rule will become effective 30 calendar days after the date of its publication in the *Federal Register*.

VII. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, Executive Order 13771, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential

economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 13771 requires that the costs associated with significant new regulations “shall, to the extent permitted by law, be offset by the elimination of existing costs associated with at least two prior regulations.” We believe that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because we do not have enough information about the effect of the final rule on small entities, we find that the final rule will have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$150 million, using the most current (2017) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

We evaluated 10 bulk drug substances for this final rule. We will place six bulk drug substances on the 503A Bulks List, and we will not place four substances on the 503A Bulks List. We expect that the rule will affect compounding pharmacies and other producers that market the affected substances or drug products made from the affected substances, consumers of drug products containing the affected substances, and payers that cover these drug products or alternative treatments. Because we lack sufficient information to quantify most of the costs and

benefits of this final rule, we also include a qualitative description of potential benefits and potential costs.

In table 1, we summarize the impacts of the final rule. The present value of the costs of the final rule equals \$3.33 million at a 7 percent discount rate and \$3 million at a 3 percent discount rate. The final rule will result in annualized costs of \$0.42 million at a 7 percent discount rate, or \$0.31 million at a 3 percent discount rate.

Table 1.--Summary of Benefits, Costs, and Distributional Effects of the Final Rule

Category		Primary Estimate	Low Estimate	High Estimate	Units			Notes
					Year Dollars	Discount Rate	Period Covered	
Benefits	Annualized Monetized (\$m/year)							
	Annualized Quantified							
	Qualitative	Potential gains or losses in consumer surplus, depending on consumer preferences for compounded drugs. Potential public health benefits from increased use of other drug products that may be more effective.						
Costs	Annualized Monetized (\$m/year)	\$0.42	\$0.27	\$0.56	2016	7%	10 years	
	Annualized Monetized (\$m/year)	\$0.31	\$0.21	\$0.42	2016	3%	10 years	
	Annualized Quantified							
	Qualitative	Costs to submit INDs for some compounded drug products.						
Transfers	Federal Annualized Monetized (\$m/year)							
	From:				To:			
	Other Annualized Monetized (\$m/year)							
	From:				To:			
Effects	State, Local, or Tribal Government: None Small Business: None Wages: None Growth: None							

We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the proposed rule. The full analysis of economic impacts is available in the docket for this final rule (Ref. 17) and at

<https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

VIII. Analysis of Environmental Impact

We have determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, FDA is not required to seek clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995.

X. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

XI. Consultation and Coordination with Indian Tribal Governments

We have analyzed this rule in accordance with the principles set forth in Executive Order 13175. We have determined that the rule does not contain policies that have substantial direct effects on one or more Indian Tribes, on the relationship between the Federal Government and Indian Tribes, or on the distribution of power and responsibilities between the Federal Government and Indian Tribes. Accordingly, we conclude that the rule does not contain policies

that have tribal implications as defined in the Executive Order and, consequently, a tribal summary impact statement is not required.

XII. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks have copyright restriction and can be viewed at Dockets Management Staff. They are not available publicly on the internet due to copyright restriction. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

*1. Food and Drug Administration, FDA Guidance for Industry on Interim Policy on Compounding Using Bulk Drug Substances Under Section 503A of the Federal Food, Drug, and Cosmetic Act, 2017; available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf>.

*2. Food and Drug Administration, Transcript of the February 23, 2015, Meeting of the Pharmacy Compounding Advisory Committee (Afternoon Session), 2015; available at <https://wayback.archive-it.org/7993/20170404155240/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444500.pdf>.

*3. Memorandum to File on Food and Drug Administration Consultations with United States Pharmacopeia, September 26, 2016.

*4. Letter from the United States Pharmacopeia to FDA, October 7, 2016.

*5. Food and Drug Administration Briefing Document for the June 17-18, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015; available at <https://wayback.archive-it.org/7993/20170405230419/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM449535.pdf>.

6. Birdsall, T.C., 1998, "5-Hydroxytryptophan: A Clinically-Effective Serotonin Precursor," *Alternative Medicine Review*, 3(4):271-80; available at <https://www.ncbi.nlm.nih.gov/pubmed/9727088>.

7. MedlinePlus, 5-HTP; available at <https://medlineplus.gov/druginfo/natural/794.html> (last reviewed November 30, 2017).

*8. Drugs.com, Prozac Side Effects, 2018; available at <https://www.drugs.com/sfx/prozac-side-effects.html>.

9. Jakoben, J.C., K.K. Katakam, A. Schou, et al., 2017, "Selective Serotonin Reuptake Inhibitors Versus Placebo in Patients with Major Depressive Disorder. A Systematic Review with Meta-Analysis and Trial Sequential Analysis." *BMC Psychiatry*, 17(1):58.

*10. Food and Drug Administration Supplemental Review of Oxitriptan, November 2018.

11. Fang, Y., Z. Qiu, W. Hu, et al., 2014. "Effect of Piracetam on the Cognitive Performance of Patients Undergoing Coronary Bypass Surgery: A Meta-Analysis." *Experimental and Therapeutic Medicine*, 7:429-434; available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3881046/>.

12. De Reuck, J. and B. Van Vleymen, 1999, "The Clinical Safety of High-Dose Piracetam--Its Use in the Treatment of Acute Stroke." *Pharmacopsychiatry*, 32 Suppl 1:33-37; available at <https://www.ncbi.nlm.nih.gov/pubmed/10338106>.

*13. Food and Drug Administration Briefing Document for the February 23-24, 2015, Meeting of the Pharmacy Compounding Advisory Committee, 2015; available at <https://wayback.archive-it.org/7993/20170405230436/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM433804.pdf>.

14. UCB Pharma SA, 2007. A multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of 9600 and 4800 mg/day piracetam (oral 800 mg tablets, b.i.d.) taken for 12 months by subjects suffering from mild cognitive impairment (MCI) Brussels: UCB, Inc. Clinical Study Summary; available at https://www.ucb.com/_up/ucb_com_patients/documents/N01001_CSS_20070907.pdf.

*15. Food and Drug Administration, Transcript of the February 24, 2015, Meeting of the Pharmacy Compounding Advisory Committee; available at <https://wayback.archive-it.org/7993/20170404155242/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/UCM444501.pdf>.

*16. Food and Drug Administration Supplemental Review of Topical Tranilast, April 25, 2016.

*17. Economic Analysis of Impacts, available at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.
List of Subjects in 21 CFR Part 216

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 216 is amended as follows:

PART 216--HUMAN DRUG COMPOUNDING

1. The authority citation for part 216 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 353a, 353b, 355, and 371.

2. Add § 216.23 to subpart B to read as follows:

§ 216.23 Bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act.

(a) The following bulk drug substances can be used in compounding under section 503A(b)(1)(A)(i)(III) of the Federal Food, Drug, and Cosmetic Act.

(1) Brilliant Blue G, also known as Coomassie Brilliant Blue G-250.

(2) Cantharidin (for topical use only).

(3) Diphenylcyclopropenone (for topical use only).

(4) N-acetyl-D-glucosamine (for topical use only).

(5) Squaric acid dibutyl ester (for topical use only).

(6) Thymol iodide (for topical use only).

(b) After balancing the criteria set forth in paragraph (c) of this section, FDA has determined that the following bulk drug substances will not be included on the list of substances that can be used in compounding set forth in paragraph (a) of this section:

(1) Oxitriptan.

(2) Piracetam.

(3) Silver Protein Mild.

(4) Tranilast.

(c) FDA will use the following criteria in evaluating substances considered for inclusion on the list set forth in paragraph (a) of this section:

(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) The available evidence of the effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and

(4) 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.

(d) Based on evidence currently available, there are inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph (a) of this section, or to establish general recognition of the safety or effectiveness of any such drug product. Any person who represents that a compounded drug made with a bulk drug substance that appears on this list is FDA approved, or otherwise endorsed by FDA generally or for a particular indication, will cause the drug to be misbranded under section 502(a) and/or 502(bb) of the Federal Food, Drug, and Cosmetic Act.

Dated: February 11, 2019.

Scott Gottlieb,

Commissioner of Food and Drugs.

[FR Doc. 2019-02367 Filed: 2/15/2019 8:45 am; Publication Date: 2/19/2019]