4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-N-3240]

# List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances (active pharmaceutical ingredients) for which there is a clinical need (the 503B Bulks List). Drug products that outsourcing facilities compound using bulk drug substances on the 503B Bulks List can qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act (FD&C Act) provided certain conditions are met. This notice identifies four bulk drug substances that FDA has considered and proposes to include on the 503B Bulks List: diphenylcyclopropenone (DPCP), glycolic acid, squaric acid dibutyl ester (SADBE), and trichloroacetic acid (TCA). This notice also identifies 19 bulk drug substances that FDA has considered and proposes not to include on the list: diazepam, dobutamine hydrochloride (HCl), dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and may be the subject of future notices.

DATES: Submit either electronic or written comments on the notice by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

*Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

*Written/Paper Submissions*

Submit written/paper submissions as follows:

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

*Instructions*: All submissions received must include the Docket No. FDA-2018-N-3240 for "List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The

second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

*Docket*: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Elizabeth Hankla, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5216, Silver Spring, MD 20993, 240-402-3359.

SUPPLEMENTARY INFORMATION:

## I. Background

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or

abbreviated new drug applications (ANDAs)), section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements).[1]

Drug products compounded that meet the conditions in section 503B are not exempt from current good manufacturing practice (CGMP) requirements in section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).[2] Outsourcing facilities are also subject to FDA inspections according to a risk-based schedule, specific adverse event reporting requirements, and other conditions that help to mitigate the risks of the drug products they compound.[3] Outsourcing facilities may or may not obtain prescriptions for identified individual patients and can, therefore, distribute compounded drugs to healthcare practitioners for "office stock," to hold in their offices in advance of patient need.[4]

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B of the FD&C Act is that the outsourcing facility may not compound a drug using a bulk drug substance unless: (1) the bulk drug substance appears on a list established by the Secretary of Health and Human Services identifying bulk drug substances for which there is a clinical need (the 503B Bulks List) or (2) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) at the time of compounding, distribution, and dispensing.[5]

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[1] Section 503B(a) of the FD&C Act.
[2] Compare section 503A(a) of the FD&C Act (21 U.S.C. 353a(a); exempting drugs compounded in accordance with that section) with section 503B(a) of the FD&C Act (not providing the exemption from CGMP requirements).
[3] Section 503B(b)(4) and (5) of the FD&C Act.
[4] Section 503B(d)(4)(C) of the FD&C Act.
[5] Section 503B(a)(2)(A) of the FD&C Act.

Section 503B of the FD&C Act directs FDA to establish the 503B Bulks List by: (1) publishing a notice in the *Federal Register* proposing bulk drug substances to be included on the list, including the rationale for such proposal; (2) providing a period of not less than 60 calendar days for comment on the notice; and (3) publishing a notice in the *Federal Register* designating bulk drug substances for inclusion on the list.[6]

In March 2019, FDA published a notice that identified two bulk drug substances, nicardipine hydrochloride and vasopressin, that were nominated for inclusion on the 503B Bulks List, and that, after consideration, FDA did not include on that list (84 FR 7383, March 4, 2019). The March 2019 notice stated that additional bulk drug substances were under evaluation and that additional substances would be the subject of future notices. This notice identifies 4 bulk drug substances that FDA has considered and proposes to include on the 503B Bulks List and 19 bulk drug substances that FDA has considered and proposes not to include on the 503B Bulks List.

For purposes of section 503B of the FD&C Act, *bulk drug substance* means an active pharmaceutical ingredient as defined in 21 CFR 207.1.[7] *Active pharmaceutical ingredient* means any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body, but the term does not include intermediates used in the synthesis of the substance.[8, 9]

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[6] Section 503B(a)(2)(A)(i)(I) to (III) of the FD&C Act.
[7] 21 CFR 207.3.
[8] Section 503B(a)(2) of the FD&C Act and 21 CFR 207.1.
[9] Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable U.S. Pharmacopeia or National Formulary monograph, if a monograph exists.

For further information about drug compounding and the background for the 503B Bulks List, see 83 FR 43877 (August 28, 2018).

## II. Methodology for Developing the 503B Bulks List

### *A. Process for Developing the List*

FDA requested nominations for specific bulk drug substances for the Agency to consider for inclusion on the 503B Bulks List in the *Federal Register* of December 4, 2013 (78 FR 72838). FDA reopened the nomination process in the *Federal Register* of July 2, 2014 (79 FR 37747) and provided more detailed information on what FDA needs to evaluate nominations for the list. On October 27, 2015 (80 FR 65770), the Agency opened a new docket, FDA-2015-N-3469, to provide an opportunity for interested persons to submit new nominations of bulk drug substances or to renominate substances with sufficient information.

As FDA evaluates bulk drug substances, it intends to publish notices for public comment in the *Federal Register* that describe the FDA's proposed position on each substance along with the rationale for that position.[10] After considering any comments on FDA's proposals regarding whether to include nominated substances on the 503B Bulks List, FDA intends to consider whether input from the Pharmacy Compounding Advisory Committee (PCAC) on the nominations would be helpful to the Agency in making its determination, and if so, it will seek PCAC input.[11] Depending on its review of the docket comments and other relevant information before the Agency, FDA may finalize its proposed determination without change, or it may finalize a modification to its proposal to reflect new evidence or analysis regarding clinical need.

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[10] This is consistent with procedure set forth in section 503B(a)(2)(A)(i) of the FD&C Act. Although the statute only directs FDA to issue a *Federal Register* notice and seek public comment when it proposes to include bulk drug substances on the 503B Bulks List, we intend to seek comment when the Agency has evaluated a nominated substance and proposes either to include or not to include the substance on the list.

[11] Section 503B of the FD&C Act does not require FDA to consult the PCAC before developing a 503B Bulks List.

FDA will then publish in the *Federal Register* a list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the *Federal Register* a list of those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a current list of all bulk drug substances it has evaluated on its website, and separately identify bulk drug substances it has placed on the 503B Bulks List and those it has decided not to place on the 503B Bulks List. FDA will only place a bulk drug substance on the 503B Bulks List where it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and any other information considered by the Agency, FDA will not place a bulk drug substance on the 503B Bulks List.

FDA intends to evaluate bulk drug substances nominated for the 503B Bulks List on a rolling basis. FDA intends to evaluate and publish in the *Federal Register* its proposed and final determinations in groups of bulk drug substances until all nominated substances that were sufficiently supported have been evaluated and either placed on the 503B Bulks List or identified as bulk drug substances that were considered but determined not to be appropriate for inclusion on the 503B Bulks List (Ref. 1).[12]

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[12] On January 13, 2017, FDA announced the availability of a revised final guidance for industry that provides additional information regarding FDA's policies for bulk drug substances nominated for the 503B Bulks List pending our review of nominated substances under the "clinical need" standard entitled "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act" ("Interim Policy"); available at https://www.fda.gov/media/94402/download.

*B. Analysis of Substances Nominated for the List*

As noted above, the 503B Bulks List will include bulk drug substances for which there is a clinical need. The Agency is currently evaluating bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the clinical need standard provided by the statute (Ref. 2).[13] In applying this standard to develop the proposals in this notice, FDA is interpreting the phrase "bulk drug substances for which there is a clinical need" to mean that the 503B Bulks List may include a bulk drug substance if: (1) there is a clinical need for an outsourcing facility to compound the drug product and (2) the drug product must be compounded using the bulk drug substance. FDA is not interpreting supply issues, such as backorders, to be within the meaning of "clinical need" for compounding with a bulk drug substance. Section 503B separately provides for compounding from bulk drug substances under the exemptions from the FD&C Act discussed above if the drug product compounded from the bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Additionally, we are not considering cost of the compounded drug product as compared with an FDA-approved drug product to be within the meaning of "clinical need."

Some of the bulk drug substances that we are addressing in this notice are components of FDA-approved drug products[14], and we therefore began our evaluation of these bulk drug substances by asking one or both of the following questions:

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[13] On March 4, 2019, FDA announced the availability of a final guidance entitled "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (84 FR 7390); available at https://www.fda.gov/media/121315/download. This guidance describes FDA policies for developing the 503B Bulks List and the Agency's interpretation of the phrase "bulk drug substances for which there is a clinical need" as it is used in section 503B of the FD&C Act. The analysis under the statutory "clinical need" standard described in this notice is consistent with the approach described in FDA's guidance.

[14] Specifically: diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl.

(1) Is there a basis to conclude, for each FDA-approved product that includes the nominated bulk drug substance, that: (a) an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and (b) the drug product proposed to be compounded is intended to address that attribute?

(2) Is there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product?

The reason for question 1 is that unless an attribute of the FDA-approved drug is medically unsuitable for certain patients, and a drug product compounded using a bulk drug substance that is a component of the approved drug is intended to address that attribute, there is no clinical need to compound a drug product using that bulk drug substance. Rather, such compounding would unnecessarily expose patients to the risks associated with drug products that do not meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. The reason for question 2 is that to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance* rather than starting with an FDA-approved drug product.

If the answer to both of these questions is "yes," there may be a clinical need for outsourcing facilities to compound using the bulk drug substance, and we would evaluate the substance further, applying the factors described below. If the answer to either of these questions is "no," we generally would not include the bulk drug substance on the 503B Bulks List, because there would not be a basis to conclude that there may be a clinical need to compound drug products using the bulk drug substance instead of administering or compounding

starting with an approved drug product. FDA did not answer "yes" to both of the threshold questions for the 19 bulk drug substances that are components of approved drug products that we are addressing in this notice. Accordingly, as explained further below, we did not proceed further in our evaluation of these substances and are proposing not to include them on the 503B Bulks List.

With respect to four bulk drug substances we are addressing in this notice that are not components of FDA-approved drug products[15], we are conducting a balancing test with four factors, considering each factor in the context of the others and balancing them, on a substance-by-substance basis, to determine whether the statutory "clinical need" standard has been met. The balancing test includes the following factors:

(a) The physical and chemical characterization of the substance;

(b) Any safety issues raised by the use of the substance in compounding;

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

(d) Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature.

The discussion below reflects FDA's consideration of these four factors where they are applicable and describes how they were applied to develop FDA's proposal to include four bulk drug substances on the 503B Bulks List.

[15] Specifically: DPCP, glycolic acid, SADBE, and TCA.

*C. Inclusion of a Bulk Drug Substance on the 503B Bulks List*

In preparing its proposal to include four substances on the 503B Bulks List, FDA considered whether the clinical need for the bulk drug substance is limited. For example, we considered whether there are safety risks associated with a drug product compounded using the bulk drug substance at a higher concentration that are not associated with compounding at a lower concentration. Similarly, we considered whether evidence that a compounded drug product may be effective is available for only certain routes of administration or dosage forms. As appropriate, and as explained further below, the Agency tailored its proposed entries on the 503B Bulks List to reflect its findings related to clinical need for each of the four bulk substances proposed for inclusion on the list. Specifically, the proposed entries would authorize use of these four bulk drug substances to compound drug products for topical dermal use only, and one of them--glycolic acid--would be authorized to compound drug products with a concentration of not more than 70 percent.

In addition, we solicit comment on whether to include a further limitation relating to the use of these bulk drug substances to compound drug products containing more than one bulk drug substance.

In developing its proposal, the Agency has considered information regarding the use of each of the four bulk drug substances to compound a drug product containing a single active ingredient and did not review information related to the use of these bulk drug substances in combination with one or more other active ingredients. For each bulk drug substance, FDA's evaluation of clinical need included a review of the physical and chemical characteristics of the substance, any safety issues raised by the use of the substance in compounding, the available evidence of effectiveness or lack of effectiveness of a drug product compounded with the

substance, and the current and historical use of the substance in compounded drug products. On this basis we have identified a clinical need to compound certain topical dermal products containing the bulk drug substances. These assessments regarding clinical need could be affected if the bulk drug substances are used in compounded products containing multiple active ingredients. In particular, the use of certain active ingredients in combination with other active ingredients in a compounded product could pose a safety risk or affect the product's effectiveness. FDA's evaluation did not take into consideration all of the possible drug products that could be made with other ingredients or evaluate the clinical need for the bulk substance in every possible combination with other substances.

We solicit comment on two options for listing the four bulk drug substances we are proposing to include on the 503B Bulks List; either: (1) to allow compounding of drug products containing only the listed bulk drug substance and no other active ingredients; or (2) to allow compounding of drug products that contain the listed bulk drug substance without limits on compounding a drug product that contains other active ingredients. Under option 2, the compounded drug product would need to meet all of the conditions of section 503B; e.g., if the outsourcing facility compounded a drug product using two bulk drug substances, both of the bulk drug substances would have to meet the conditions in section 503B(a)(2).

## III. Substances Considered and Proposed for Inclusion on the 503B Bulks List

Because the substances in this section are not components of FDA-approved drug products, we applied the balancing test described above. The four bulk drug substances that have been evaluated and that FDA is proposing to place on the 503B Bulks List are DPCP,

glycolic acid, SADBE, and TCA. The reasons for FDA's proposals are included below (Refs. 3 to 6).[16]

*A. Diphenylcyclopropenone (DPCP)*

DPCP was nominated as a bulk drug substance for the 503B Bulks List to compound drug products for topical use at variable concentrations, usually 2 percent, in the treatment of alopecia areata.[17] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated DPCP for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B of the FD&C Act, considering data and information regarding the physical and chemical characterization of DPCP, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding (Ref. 3).

DPCP is well characterized but there are concerns about stability and consistency in product quality. Although there are still gaps in the evidence for DPCP's safety and effectiveness, including a lack of long-term safety data, substantial human safety data have been collected and clinicians worldwide have gained experience in the use of DPCP to treat alopecia areata. DPCP has been used for several decades to compound drug products for dermatologists to treat alopecia areata and continues to be used for this purpose. The reported adverse effects are related to DPCP's mechanism of therapeutic action as a sensitizer, causing allergic contact dermatitis in treated patients. Alopecia areata may not respond adequately to available

[16] In addition to the nominations for the 503B Bulks List, the Agency considered data and information from its earlier evaluations regarding the use of these bulk drug substances for the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (the 503A Evaluations). FDA also considered a report provided by the University of Maryland Center of Excellence in Regulatory Science and Innovation and conducted a search for relevant scientific literature and safety information, focusing on materials published or submitted to FDA since the 503A Evaluations.

[17] See Docket No. FDA-2013-N-1524, document no. FDA-2013-N-1524-1363.

treatments. DPCP can be a potentially effective agent for patients who have failed FDA-approved and other therapies for this condition.

On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of DPCP weigh in favor of including this substance on the 503B Bulks List. Accordingly, we propose adding DPCP to the 503B Bulks List for topical dermal use only. Nominators did not submit, and we have not identified, significant evidence to support use in other routes of administration.

*B. Glycolic Acid*

Glycolic acid was nominated as a bulk drug substance for the 503B Bulks List to compound drug products for topical use at concentrations ranging from 0.08 to 70 percent for the treatment of hyperpigmentation and photodamaged skin.[18] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated glycolic acid for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, considering data and information regarding the physical and chemical characterization of glycolic acid, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding (Ref. 4).

Glycolic acid, also known as hydroxyacetic acid, is physically and chemically well characterized. When used in high concentrations, glycolic acid causes local effects that are typical of a strong acid, such as dermal and eye irritation. Reported adverse reactions were

[18] See Docket No. FDA-2015-N-3469, document nos. FDA-2015-N-3469-0035 and FDA-2015-N-3469-0123. One of the nominations also states that prescribers may want glycolic acid compounds in other formulations to treat other conditions but does not identify the conditions or formulations. It also refers to the use of glycolic acid in combination with other ingredients and, in particular, to compounding a formulation containing hydroquinone 6 percent and tretinoin 0.1 percent. Information submitted with this nomination relevant to compounding with glycolic acid for the treatment of hyperpigmentation disorders and photodamaged skin was considered. FDA's evaluation does not consider whether there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances hydroquinone or tretinoin, or other bulk drug substances.

generally limited in duration and readily manageable. There is no information available on long-term outcomes. The available data on short-term outcomes do not raise major safety concerns associated with the topical use of glycolic acid.

Data from controlled clinical trials have shown consistently positive results in the treatment of epidermal melasma or other forms of hyperpigmentation. The available evidence suggests that there is a role for glycolic acid in the treatment of melasma, typically as a second line treatment. There is also some evidence indicating that glycolic acid may be effective for the mitigation of manifestations of photodamaged skin. Glycolic acid has been used for several decades to compound drug products for dermatologists and continues to be used for this purpose. Conclusions regarding each of these factors are for use at concentrations up to 70 percent; data and evidence regarding use of higher concentrations are very limited.

On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of glycolic acid weigh in favor of including this substance on the 503B Bulks List at concentrations up to 70 percent. Accordingly, we propose adding glycolic acid to the 503B Bulks List for topical dermal use in concentrations up to 70 percent. Nominators did not submit, and we have not identified, significant evidence to support use in other routes of administration or higher concentrations.

*C. Squaric Acid Dibutyl Ester (SADBE)*

SADBE was nominated as a bulk drug substance for the 503B Bulks List to compound drug products for topical use at variable concentrations, ranging from 2 percent initially to 0.0001 percent to 0.001 percent for maintenance, for the treatment of alopecia areata and warts.[19] The nominated bulk drug substance is not a component of an FDA-approved drug product. We

[19] See Docket No. FDA-2013-N-1524, document no. FDA-2013-N-1524-1363.

evaluated SADBE for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, considering data and information regarding the physical and chemical characterization of SADBE, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding (Ref. 5).

SADBE is well-characterized but there are concerns about stability and consistency in product quality. There is a lack of adequate nonclinical data, long-term safety data, and safety information about use in specific populations such as pregnant and lactating women. Despite these data gaps, considerable human safety data have accumulated over the past 40 years from its use in compounding drug products for dermatologists to treat alopecia areata and resistant non-genital warts and from reports for its use internationally. The reported adverse effects are related to SADBE's mechanism of therapeutic action as a sensitizer causing allergic contact dermatitis in treated patients.

In addition, both alopecia areata and warts may not respond adequately to available treatments. SADBE can be a potentially effective agent for patients who have failed FDA-approved and other therapies for these conditions. We recognize that treatment with SADBE requires initial sensitization and typical protocols involve a SADBE concentration of 2 percent, but lower concentrations may be used in other patients.

On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of SADBE weigh in favor of including this substance on the 503B Bulks List. Accordingly, we propose adding SADBE to the 503B Bulks List for topical dermal use only. Nominators did not submit, and we have not identified, significant evidence to support use in other routes of administration.

*D. Trichloroacetic Acid (TCA)*

TCA was nominated as a bulk drug substance for the 503B Bulks List to compound drug products for topical use at concentrations ranging from 6 percent to 20 percent as a chemical skin peeling agent for the treatment of acne and melasma.[20] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated TCA for potential inclusion on the 503B Bulks List under the clinical need standard in section 503B, considering data and information regarding the physical and chemical characterization of TCA, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding (Ref. 6).

TCA is well characterized in its physical and chemical properties. Nonclinical evidence suggests that topical use of TCA does not raise serious safety issues for humans. Although there have been no clinical trials specifically designed to address the safety of TCA, safety assessments were among the study procedures in several clinical trials and reports of adverse reactions have included burning, pain, erythema, hyperpigmentation, and hypopigmentation. More serious adverse reactions reported were ulcerations, scarring, and pustules. Adverse events were reported more frequently with higher concentrations. Several studies indicate that TCA may be effective as a chemical peel for the treatment of acne (Ref. 7) and melasma (Ref. 8), but there is a lack of evidence comparing TCA to FDA-approved drug products for those uses. TCA has been used, in the United States and worldwide, for dermatologic conditions for over 40 years and for at least 20 years in pharmacy compounding.

On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of TCA weigh in favor of including this substance on the 503B Bulks

[20] See Docket No. FDA-2018-D-1067, document no. FDA-2018-D-1067-0005.

List. Accordingly, we propose adding TCA to the 503B Bulks List for topical dermal use only. Nominators did not submit, and we have not identified, significant evidence to support use in other routes of administration.

## IV. Substances Evaluated and Not Proposed for Inclusion on the 503B Bulks List

Because the substances in this section are components of FDA-approved drug products, we considered one or both of the following questions: (1) is there is a basis to conclude that an attribute of each FDA-approved drug product containing the bulk drug substance makes each one medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation, and the drug product proposed to be compounded is intended to address that attribute and (2) is there a basis to conclude that the drug product proposed to be compounded must be compounded using a bulk drug substance.

The 19 bulk drug substances that have been evaluated and that FDA is proposing not to place on the list are as follows: diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium thiosulfate, and verapamil HCl. The reasons for FDA's proposals are included below.

### *A. Diazepam*

Diazepam has been nominated for inclusion on the 503B Bulks List to compound drug products that are used for alcohol withdrawal syndrome, anxiety, and as premedication before surgery, endoscopic procedures, and cardioversion, among other conditions.[21] The proposed route of administration is intravenous or intramuscular, the proposed dosage form is a preserved

[21] See Docket No. FDA-2013-N-1524, document no. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

solution, and the proposed concentration is 5 milligrams per milliliter (mg/mL). The nominators propose to compound a preserved solution. However, they fail to acknowledge that there is an FDA-approved formulation of diazepam that is preserved and do not explain why that formulation would be medically unsuitable for certain patients. The nominations state that diazepam might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 072079). FDA-approved diazepam is available as a preserved 10 mg/2 mL (5 mg/mL) and 50 mg/10 mL (5 mg/mL) solution for intravenous or intramuscular administration.[22, 23, 24]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preserved 5 mg/mL solution products is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product (also a preserved 5 mg/mL solution) is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

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[22] See, e.g., ANDA 072079 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/4e800d0d-2181-49b1-a2c8-4c6c49edd83a/4e800d0d-2181-49b1-a2c8-4c6c49edd83a.xml.

[23] Per the label for ANDA 072079, each mL contains 5 mg diazepam, 40 percent propylene glycol, 10 percent alcohol, 5 percent sodium benzoate and benzoic acid added as buffers, and 1.5 percent benzyl alcohol added as a preservative.

[24] Diazepam is also approved as an oral tablet, oral concentrate, oral solution, and rectal gel.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using diazepam and approved drug products containing diazepam, there is nothing for FDA to evaluate under question 2.

*B. Dobutamine HCl*

Dobutamine HCl has been nominated for inclusion on the 503B Bulks List to compound drug products for ionotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.[25] The proposed route of administration is intravenous (IV), the proposed dosage form is an injection, and the proposed concentrations are 1 mg/mL, 2 mg/mL, and 4 mg/mL in various volumes of IV infusions (large volume parenterals). The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 074086 and NDA 020201). FDA has approved dobutamine drug products as EQ 50 mg base/100 mL (EQ 0.5 mg base/mL), EQ 100 mg base/100 mL (EQ 1 mg base/mL), EQ 200 mg base/100 mL (EQ 2 mg base/mL), and EQ 400 mg base/100 mL (EQ 4 mg base/mL) ready-to-administer forms (e.g., no further dilutions needed) for intravenous administration and as an EQ 12.5mg base/mL single-dose vial that must be diluted prior to infusion.[26, 27]

1. Suitability of FDA-Approved Drug Product(s)

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[25] See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0032.
[26] See, e.g., ANDA 074086 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/7b9ea626-7073-2e77-e053-2a91aa0a9215/7b9ea626-7073-2e77-e053-2a91aa0a9215.xml.
[27] See, e.g., NDA 020201 (ready-to-use version) labeling available as the date of this notice at https://www.accessdata.fda.gov/spl/data/d1873a74-56e6-4a01-8e4d-875789e5e344/d1873a74-56e6-4a01-8e4d-875789e5e344.xml.

The nomination does not explain why an attribute of each of the FDA-approved EQ 12.5 mg base/mL solution for dilution for intravenous administration products and each of the approved EQ 1 mg base/mL, EQ 2 mg base/mL, and EQ 4 mg base/mL ready-to-administer forms is medically unsuitable for certain patients, or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nomination does not identify specific differences between drug products that would be compounded using dobutamine HCl and approved drug products containing dobutamine HCl, there is nothing for FDA to evaluate under question 2.

*C. Dopamine HCl*

Dopamine HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat cardiogenic shock, congestive heart failure, decreased cardiac output, and renal failure, among other conditions.[28] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution, and the proposed concentration is 80 mg/mL. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of dopamine HCl available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that dopamine HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component

[28] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

of FDA-approved drug products (e.g., ANDA 207707). FDA-approved dopamine HCl is available as a single-dose, preservative-free 40 mg/mL or 80 mg/mL solution for intravenous administration.[29, 30]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preservative-free 80 mg/mL solution products is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using dopamine HCl and approved drug products containing dopamine HCl, there is nothing for FDA to evaluate under question 2.

*D. Edetate Calcium Disodium*

Edetate calcium disodium dihydrate has been nominated for inclusion on the 503B Bulks List to compound drug products that treat cardiovascular disease, diabetes, hypercholesterolemia, arthritis, cancer, and chronic renal failure, among other conditions.[31] The proposed route of administration is slow intravenous, the proposed dosage form is a preservative-free injection, and

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[29] See, e.g., ANDA 207707 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/d2927591-5fe5-4704-9091-82ab08bb792b/d2927591-5fe5-4704-9091-82ab08bb792b.xml.

[30] According to the label for ANDA 207707, each mL contains metabisulfite 9 mg added as an antioxidant, citric acid, anhydrous 10 mg, sodium citrate, and dihydrate 5 mg added as a buffer. May contain additional citric acid and/or sodium citrate for pH adjustment.

[31] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2302, FDA-2013-N-1524-2301, FDA-2013-N-1525-0225, FDA-2013-N-1524-2305, and FDA-2013-N-1524-2297.

the proposed concentration is 200 mg/mL. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of edetate calcium disodium available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominated bulk drug substance is a component of an FDA-approved drug product (NDA 008922).[32] FDA-approved edetate calcium disodium is available as a preservative-free 200 mg/mL injection for intravenous and intramuscular administration.[33, 34]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of the FDA-approved preservative-free 200 mg/mL injection is medically unsuitable for certain patients or identify an attribute of the approved drug product that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using edetate calcium disodium and the approved drug product containing edetate calcium disodium, there is nothing for FDA to evaluate under question 2.

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[32] In the nominations, the name of the nominated substance is listed as "edetate calcium disodium dihydrate." Since the nominated dosage form is an injection, "edetate calcium disodium" and "edetate calcium disodium dihydrate" result in the same entity when in solution.

[33] See NDA 008922 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/143830d7-46a5-49a3-b8b2-457a59533008/143830d7-46a5-49a3-b8b2-457a59533008.xml.

[34] Per the label for NDA 008922, edetate calcium disodium dihydrate is available in a preservative-free ampule. Each 5 ml ampule contains 1,000 mg of edetate calcium disodium (equivalent to 200 mg/ml) in water for injection.

*E. Folic Acid*

Folic acid has been nominated for inclusion on the 503B Bulks List to compound drug products that treat megaloblastic and macrocytic anemias.[35] The proposed routes of administration are intravenous, intramuscular, and subcutaneous, the proposed dosage forms are injection solutions, and the proposed concentration is 5 mg/mL. The nomination states that folic acid might also be used to compound other drug products but does not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 089202). FDA-approved folic acid is available as a 50 mg/10 mL (5 mg/mL) solution for intravenous, intramuscular, and subcutaneous administration.[36, 37]

1. Suitability of FDA-Approved Drug Product(s)

The nomination does not explain why an attribute of each of the FDA-approved 5 mg/mL solution products for intravenous, intramuscular, and subcutaneous administration is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

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[35] See Docket No. FDA-2013-N-1524, document no. FDA-2013-N-1524-2292.
[36] See, e.g., ANDA 089202 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/d1a4f664-040d-4c6d-b137-e0a0a9e7bf26/d1a4f664-040d-4c6d-b137-e0a0a9e7bf26.xml.
[37] Folic acid is also approved in as a single ingredient as an oral tablet.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nomination does not identify specific differences between drug products that would be compounded using folic acid and approved drug products containing folic acid, there is nothing for FDA to evaluate under question 2.

### *F. Glycopyrrolate*[38]

Glycopyrrolate bromide has been nominated for inclusion on the 503B Bulks List to compound drug products that treat cardiac dysrhythmia, surgically induced or drug-induced vagal reflex, and peptic ulcer disease, among other conditions.[39] The proposed route of administration is intravenous, the proposed dosage forms are both a preservative-free and a preserved solution, and the proposed concentration is 0.2 mg/mL. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of glycopyrrolate available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that glycopyrrolate might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., NDA 210997). FDA-approved glycopyrrolate is available as a 0.2 mg/mL in 1 mL or 2

[38] One nominator nominated "Glycopyrrolate, USP" and the other nominator nominated "Glycopyrrolate Bromide." The UNII code for both nominations (V92SO9WP2I) corresponds to the chemical formula for glycopyrrolate bromide (C19H28NO3.Br). The official FDA and USP nonproprietary name for glycopyrrolate bromide is "glycopyrrolate." Therefore, if finalized, glycopyrrolate (not glycopyrrolate bromide) will not be added to the 503B Bulks List.

[39] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

mL preserved and preservative-free, single-dose vials for intramuscular or intravenous administration.[40, 41, 42]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of the FDA-approved 0.2 mg/mL preservative-free and the FDA-approved preserved solutions for intramuscular or intravenous administration are medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using glycopyrrolate and approved drug products containing glycopyrrolate, there is nothing for FDA to evaluate under question 2.

*G. Hydroxyzine HCl*

Hydroxyzine HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat alcohol withdrawal syndrome, analgesia in labor, pre- and postpartum reduction of narcotic use, and relief of anxiety, among other conditions.[43] The proposed route of administration is intramuscular, the proposed dosage form is a preserved solution, and the

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[40] See, e.g., NDA 210997 and ANDA 208973 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/6a379327-0f29-44a4-ba4f-54cb9379f854/6a379327-0f29-44a4-ba4f-54cb9379f854.xml and https://www.accessdata.fda.gov/spl/data/fdebc248-87d3-4afd-a5ed-592fcaddab1c/fdebc248-87d3-4afd-a5ed-592fcaddab1c.xml.

[41] Per the label for NDA 210997, glycopyrrolate is available in a preservative-free, single-dose vial. Per the label for ANDA 208973, glycopyrrolate is available in preserved, single-dose and multiple-dose vials.

[42] Glycopyrrolate is also approved oral tablet, oral solution, and for inhalation as a single ingredient.

[43] See Docket No FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

proposed concentration is 50 mg/mL. The nominators proposed to compound a preserved solution. However, they failed to acknowledge that there is a preserved formulation of hydroxyzine HCl available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that hydroxyzine HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 087408). FDA-approved hydroxyzine HCl is available as a preserved 50 mg/mL solution for intramuscular administration.[44, 45, 46]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of the FDA-approved preserved 50 mg/mL hydroxyzine HCl solution for intramuscular administration is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using hydroxyzine HCl and the approved drug product containing hydroxyzine HCl, there is nothing for FDA to evaluate under question 2.

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[44] See, e.g., ANDA 087408 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/4d9d37b0-7fa0-47e1-8414-c2b86f83fe73/4d9d37b0-7fa0-47e1-8414-c2b86f83fe73.xml.

[45] Per the label for ANDA 087408, each mL contains hydroxyzine HCl 25 mg or 50 mg, benzyl alcohol 0.9 percent, and water for injection q.s. pH is adjusted with sodium hydroxide and/or hydrochloric acid.

[46] Hydroxyzine HCl is also approved as an oral tablet and as an oral syrup.

*H. Ketorolac Tromethamine*

Ketorolac tromethamine has been nominated for inclusion on the 503B Bulks List to compound drug products for seasonal allergic conjunctivitis, short-term pain, pain in the eye, and extraction of cataract.[47] The proposed route of administration is intravenous and intramuscular, the proposed dosage form is a preserved solution, and the proposed concentration is 30 mg/mL. The nominators proposed to compound a preserved solution. However, they failed to acknowledge that there is a preserved formulation of ketorolac tromethamine available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that ketorolac tromethamine might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 209900). FDA-approved ketorolac tromethamine is available as a 15 mg/mL or 30 mg/mL solution for intravenous and intramuscular administration.[48, 49, 50]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preserved 30 mg/mL solution products is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them

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[47] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.
[48] See, e.g., ANDA 209900 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/f7e12067-6ba2-48d8-abac-7b4d9a6822f3/f7e12067-6ba2-48d8-abac-7b4d9a6822f3.xml.
[49] According to the label for ANDA 209900, the solution contains 10 percent (w/v) alcohol USP, and 6.68 mg, 4.35 mg, and 8.70 mg, respectively, of sodium chloride in sterile water. The pH range is 6.9 to 7.9 and is adjusted with sodium hydroxide and/or hydrochloric acid.
[50] Ketorolac tromethamine is also approved as a single ingredient in an ophthalmic drop, a nasal spray, and an oral tablet.

medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using ketorolac tromethamine and approved drug products containing ketorolac tromethamine, there is nothing for FDA to evaluate under question 2.

*I. Labetalol HCl*

Labetalol HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that control blood pressure in severe hypertension.[51] The proposed route of administration is intravenous, the proposed dosage form is an injection solution, and the proposed concentration is 5 mg/mL. The nomination states that labetalol HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 075240). FDA-approved labetalol hydrochloride is available as a 100 mg/20 mL (5 mg/mL) and 200 mg/40 mL (5 mg/mL) solution for dilution for intravenous administration.[52, 53]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved 5 mg/mL solution for dilution products is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes

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[51] See Docket No. FDA-2013-N-1524, document no. FDA-2013-N-1524-2292.
[52] See, e.g., ANDA 075240 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/d92ec06a-794d-4951-8173-b7fa7c9a66bd/d92ec06a-794d-4951-8173-b7fa7c9a66bd.xml.
[53] Labetalol hydrochloride is also approved as an oral tablet.

them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using labetalol HCl and approved drug products containing labetalol HCl, there is nothing for FDA to evaluate under question 2.

*J. Mannitol*

Mannitol has been nominated for inclusion on the 503B Bulks List to compound drug products for treatment of acute renal failure, inhalation bronchial challenge testing, and irrigation of the urinary bladder, among other conditions.[54] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution, and the proposed concentration is 25 percent. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of mannitol available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that mannitol might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., NDA 016269). FDA-approved mannitol is available as a preservative-free solution in water for injection in various concentrations,

[54] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

including a 25 percent concentration in a flip-top vial for administration by intravenous infusion only.[55, 56, 57]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved 25 percent preservative-free solution products is medically unsuitable for certain patients or identify an attribute of the approved drug product that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using mannitol and approved drug products containing mannitol, there is nothing for FDA to evaluate under question 2.

*K. Metoclopramide HCl*

Metoclopramide HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat chemotherapy-induced nausea and vomiting, diabetic gastroparesis, gastroesophageal reflux disease, and postoperative nausea and vomiting, among other conditions.[58] The proposed routes of administration are intravenous and intramuscular, the proposed dosage forms are both a preservative-free and a preserved suspension and the proposed

[55] See, e.g., NDA 016269 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/785b3a4e-c632-48c6-9fc9-b1b4e7d5d885/785b3a4e-c632-48c6-9fc9-b1b4e7d5d885.xml.
[56] Per the label for NDA 016269, the solutions contain no bacteriostat, antimicrobial agent or added buffer (except for pH adjustment) and each is intended only as a single-dose injection.
[57] Mannitol is also approved as a single ingredient as a solution for irrigation and as a powder for inhalation.
[58] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

concentration is 5 mg/mL. The nominators proposed to compound both preservative-free and preserved suspensions. However, they failed to acknowledge that there is a preservative-free formulation of metoclopramide HCl available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that metoclopramide HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 073118). FDA-approved metoclopramide HCl is available as a preservative-free 10 mg/2 mL (5 mg/mL) solution for intravenous or intramuscular administration.[59, 60, 61]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preservative-free 10 mg/2 mL (5 mg/mL) solution products for intravenous or intramuscular administration is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. In particular, the nominations do not identify any data or information indicating that there are some patients who need a preserved product rather than the approved preservative-free products. In addition, the nominations do not identify any data or information indicating that there are some patients who need a suspension rather than a solution for intravenous and intramuscular administration. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them

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[59] See, e.g., ANDA 073118 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/93db98f7-b687-432f-810a-5c4da6d874ab/93db98f7-b687-432f-810a-5c4da6d874ab.xml.

[60] Per the label for ANDA 073118, the solution is preservative-free and is intended for intravenous or intramuscular administration.

[61] Metoclopramide is also approved as an oral solution and as a tablet.

medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations have not identified a population for whom the approved products would be medically unsuitable, FDA has not evaluated whether the proposed preserved drug products containing metoclopramide HCl must be compounded from bulk drug substances rather than using the approved drug product.

*L. Moxifloxacin HCl*

Moxifloxacin HCl has been nominated for inclusion on the 503B Bulks List in combination with other bulk drug substances, including triamcinolone acetonide and vancomycin HCl, as a topical ophthalmic and as an intravitreal injection in patients who undergo cataract surgery.[62] According to the nomination, the compounded products are as follows:

(1) Moxifloxacin hydrochloride (0.2ml-0.3ml; 1mg/ml in combination with other compounds);

(2) Moxifloxacin hydrochloride in a formulation with triamcinolone "acetonidenide"[63] (0.1 mg/mL to 50.0 mg/ml 165 mcg injection); and

(3) Moxifloxacin hydrochloride in a formulation with triamcinolone "aceton[id]e" and vancomycin hydrochloride (0.1 mg/mL to 50.0 mg/ml 165 mcg injection).[64]

The nominated bulk drug substance is a component of FDA-approved drug products. FDA-approved moxifloxacin HCl is available as an EQ 0.5 percent base ophthalmic solution

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[62] See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0004.
[63] We assume this refers to triamcinolone acetonide.
[64] The nomination did not propose to compound drug products using moxifloxacin as a single active ingredient, and FDA's evaluation does not consider such uses.

under two separate NDAs (Vigamox, NDA 021598; Moxexa, NDA 022428) and various ANDAs.[65] In addition, FDA-approved moxifloxacin HCl is available as an EQ 400 mg base/250 mL (EQ 1.6 mg base/mL) solution for intravenous administration (e.g. ANDA 205833).[66, 67]

The nomination proposes to combine moxifloxacin HCl with two other bulk drug substances, both of which are components of FDA-approved products. Triamcinolone acetonide (Triesence, NDA 022048) is available as a 40 mg/mL suspension for intravitreal administration.[68, 69] Vancomycin HCl is available as an intravenous solution and as a lyophilized powder for preparing intravenous infusions in various strengths (e.g. ANDA 205694).[70, 71]

1. Suitability of FDA-Approved Drug Product(s)

a. Moxifloxacin HCl in combination with "other compounds"

The proposal to combine moxifloxacin HCl with "other compounds" will not be considered further. The nomination does not identify the "other compounds"[72] that the nominator proposes to combine with moxifloxacin HCl in a compounded drug product, or other attributes of those products (e.g., proposed dosage strength(s)). Nor does the nomination identify

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[65] See, NDA 021598 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/f9febc6f-db6d-44e8-9730-f7c1a2354d71/f9febc6f-db6d-44e8-9730-f7c1a2354d71.xml

[66] See, ANDA 205833 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/840eeb54-1874-4831-8c55-38efa1099c69/840eeb54-1874-4831-8c55-38efa1099c69.xml.

[67] Moxifloxacin is also available as a single ingredient as an oral tablet.

[68] See, NDA 022048 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/5561cb6d-1ddb-4b3a-a131-efc210f35e6b/5561cb6d-1ddb-4b3a-a131-efc210f35e6b.xml.

[69] Triamcinolone acetonide is also available as a single ingredient in topical, injectable, nasal, and dental products.

[70] ANDA 205694 is available as a preservative free lyophilized powder, for preparing intravenous infusions, in vials each containing vancomycin HCl EQ 500 mg base/vial and EQ 1 gram base/vial. See, ANDA 205694 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/028f4949-396d-d15b-8fc3-2bf69daf67f2/028f4949-396d-d15b-8fc3-2bf69daf67f2.xml.

[71] Vancomycin HCl is also available as a single ingredient as an oral capsule and powder for oral solution.

[72] We understand the term "other compounds" to refer to other bulk drug substances that would be contained in the compounded drug.

any attribute of the FDA-approved drug products that makes them medically unsuitable to treat certain patients for a condition and that the proposed compounded drugs are intended to address.

b. Moxifloxacin HCl in combination with triamcinolone acetonide for injection

The nomination states that the FDA-approved products are drops, and that a compounded intravitreal product is needed for patients recovering from cataract surgery. Specifically, the nomination states that "intravitreal placement of the compounded drug" during surgery, relative to the post-surgical installation of "a number of" topical medications, "avoids confusion of post-operative treatment to patients who undergo cataract surgery." The nomination states, further, that "the length of a typical postoperative drop regimen is further complicated by the different daily dosing regiments of various medications, which can cause confusion for patients because age [sic] and physical handicaps. " Thus, the proposed clinical need for compounding from bulk moxifloxacin HCl and triamcinolone acetonide is to prepare an intraoperative injection for patients who would have difficulty with topical administration of the approved topical products post-operatively.

The nomination does not provide supporting data or information for its statement about the medical unsuitability of FDA-approved topical products to treat patients post-operatively. [73] We take no position at this time on whether any such unsuitability exists. To the extent there may be patients for whom the FDA-approved topical dosage forms are medically unsuitable post-operatively, the nomination does not acknowledge that there are FDA-approved products containing moxifloxacin HCl and triamcinolone acetonide that are available as intravitreal injections or could be used to prepare such injections for patients undergoing cataract surgery.

[73] For example, the nomination did not provide supporting data or information to demonstrate a medical unsuitability for certain patients, or to identify which patients might find the topical products medically unsuitable and under what conditions.

Nor does the nomination explain how the drugs it proposes to compound from bulk drug substances are intended to address an attribute of these approved drugs.

Specifically, the nomination does not acknowledge that there is an FDA-approved triamcinolone acetonide product for intravitreal injection (Triescence, NDA 022048), nor does it identify an attribute of this approved product that would make it medically unsuitable for the proposed use. Nor does the nomination identify an attribute of the FDA-approved drug products that contain moxifloxacin HCl (e.g., Vigamox NDA 021598 or moxifloxacin HCl solution for intravenous administration (e.g. ANDA 205833)) that would make them medically unsuitable for the proposed use. For example, if there are patients for whom products for topical administration would be medically unsuitable, the nomination does not explain or provide support for the view that the approved products, or drug products prepared using the approved products, could not be injected sequentially during cataract surgery to address the same clinical condition.[74, 75, 76] Further, the nomination does not explain or provide support for the view that compounding a drug product for injection that contains both moxifloxacin HCl and triamcinolone acetonide, in a single solution, is intended to change some attribute of the approved drugs that makes the

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[74] In making this observation, we do not suggest that the approved drug products, or products prepared from them, are approved for the use proposed by the nomination. Here we are asking a limited, threshold question to determine whether there might be clinical need for a compounded drug product, by asking what attributes of the approved drug the proposed compounded drug would change, and why. Asking this question helps ensure that if a bulk drug substance is included on the 503B Bulks List, it is to compound drugs that include a needed change to an approved drug product rather than to produce drugs without such a change. Because our answer to question (1) is "no", we do not evaluate the available evidence of effectiveness or lack of effectiveness of a drug product compounded with moxifloxacin HCl and triamcinolone acetonide. Vigamox and moxifloxacin HCl for injection have not been demonstrated to be safe and effective as an intravitreal injection to treat any condition or disease. FDA-approved Triesence is an intravitreal injection product, approved for a different use than what is proposed in the nomination.

[75] In 2020, based on FDA's review of safety data and information, the Agency approved a supplemental application to remove a warning from the Vigamox labeling against intraocular injection.

[76] Typically, endotoxin testing is not required for topically administered ophthalmic products (e.g. Vigamox). See USP General Chapter <771> Ophthalmic Products-Quality Tests. Under CGMP requirements for outsourcing facilities each shipment of each lot of components must be tested to verify identity and evaluated for conformity with appropriate specifications before use (see 21 CFR 211.84). Appropriate specifications for components in products intended for intravitreal use include bacterial endotoxin level.

approved drugs medically unsuitable to treat certain patients who have cataract surgery. In general, the combination of two or more active ingredients to allow for the administration of fewer drug products is not likely to constitute clinical need, and we are not aware of a basis to conclude that there is clinical need to make the combination proposed by this nomination.

Accordingly, with respect to the moxifloxacin HCl with triamcinolone acetonide for intraocular injection products proposed to be compounded, FDA finds no basis to conclude that an attribute of the FDA-approved products make them medically unsuitable to treat certain patients who undergo cataract surgery and that the proposed compounded drugs are intended to address.

c. Moxifloxacin HCl with triamcinolone acetonide and vancomycin HCl for injection

The nomination states that there is a clinical need for the proposed compounded drug products to prepare an intraoperative injection for patients who would have difficulty with topical administration of the approved products post-operatively. As discussed above, the nomination does not identify an attribute of the FDA-approved products containing moxifloxacin HCl and triamcinolone acetonide that would make them medically unsuitable for the proposed use. The nomination also does not acknowledge the availability of FDA-approved vancomycin HCl for injection products (e.g., ANDA 62663), or identify an attribute of the FDA-approved products that would make them medically unsuitable for the proposed use. For example, if there are patients for whom products for topical administration would be medically unsuitable, the nomination does not explain or provide support for the view that the approved products, or drug products prepared using the approved products, could not be injected sequentially during cataract

surgery.[77] Further, the nomination does not explain or provide support for the view that compounding a drug product for injection that contains moxifloxacin HCl, triamcinolone acetonide, and vancomycin HCl, in a single solution, is intended to address any attribute of the approved drugs that make them medically unsuitable to treat certain patients who have cataract surgery.[78]

Accordingly, with respect to the moxifloxacin HCl with triamcinolone acetonide and vancomycin HCl for injection product proposed to be compounded, FDA finds no basis to conclude that there are attributes of the FDA-approved products that make them medically unsuitable to treat certain patients who undergo cataract surgery.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because we are proposing not to include moxifloxacin HCl on the 503B Bulks list for the reasons described above, we do not consider whether there is a basis to conclude that the drug products proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product.

3. Additional Comments

For the reasons stated above, we did not evaluate this nomination using the factors that we considered for our evaluation in section II.B above. However, we note that the nomination provided no data or support regarding the evidence or lack of evidence of efficacy for the drug products it proposed to compound using bulk drug substances, or regarding the evidence of safety. The nomination also did not provide information regarding the extent of historic and current use of the drug products it proposed to compound.

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[77] In noting this issue, we do not mean to suggest or imply that the approved drug products, or products prepared from them, are approved for the use proposed by the nomination. See fn. 71 above.
[78] See fn. 73, above.

Further, the prophylactic use of intraocular vancomycin, alone or in a compounded drug combining multiple active ingredients, during cataract surgery is associated with the risk of hemorrhagic occlusive retinal vasculitis (HORV),[79] a rare, potentially blinding postoperative complication that has been observed after intraocular injection of vancomycin formulations toward the end of otherwise uncomplicated cataract surgeries.[80] On September 28, 2017, FDA approved a supplemental new drug application that adds a subsection about HORV to the WARNINGS section in the labeling of Vancomycin Injection, USP. The warning states:

> Hemorrhagic occlusive retinal vasculitis, including permanent loss of vision, occurred in patients receiving intracameral or intravitreal administration of vancomycin during or after cataract surgery. The safety and efficacy of vancomycin administered by the intracameral or the intravitreal route have not been established by adequate and well-controlled trials. Vancomycin is not indicated for prophylaxis of endophthalmitis.

Most of the bulk drug substance nominations FDA has evaluated to date have only proposed to compound drug products containing a single active ingredient. This nomination proposed to compound drug products containing more than one active ingredient. If FDA finalizes its proposal not to include moxifloxacin HCl on the 503B Bulks List, we intend to remove the substance from Category 1 for purposes of the Interim Policy, which would mean that drug products compounded using the bulk drug substance moxifloxacin HCl, including the proposed compounded products addressed in this notice, would fall outside the enforcement discretion described in the Interim Policy. However, if the proposal not to include moxifloxacin

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[79] See FDA's compounding risk alert current as of June 21, 2018, at https://www.fda.gov/drugs/human-drug-compounding/case-hemorrhagic-occlusive-retinal-vasculitis-horv-following-intraocular-injections-compounded.
[80] Id.

HCl on the 503B Bulks List is finalized, FDA would not remove triamcinolone acetonide or vancomycin HCl from Category 1 at that time as a result, because we are not currently in the process of reviewing nominations for those substances or any supporting data or information they contain. Nominations for vancomycin and triamcinolone acetonide, if they are not withdrawn, remain the subject of future evaluations. Finally, if FDA determines there is a clinical need for outsourcing facilities to use bulk drug substances to compound the proposed drug products, we would include each substance, as appropriate, on the 503B Bulks List at the time that final determination is made.

*M. Nalbuphine HCl*

Nalbuphine HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that are used for general anesthesia and to treat moderate to severe pain as a preoperative, postoperative, and obstetrical analgesia.[81] The proposed routes of administration are intravenous, intramuscular, and subcutaneous, the proposed dosage form is a preservative-free solution, and the proposed concentrations are 10 mg/mL and 20 mg/mL. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of nalbuphine HCl available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that nalbuphine HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 070914). FDA-approved nalbuphine HCl is available as a

[81] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2298 and FDA-2013-N-1524-2292.

preservative-free 10 mg/mL and 20 mg/mL solution for intravenous, intramuscular, and subcutaneous administration.[82, 83]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preservative-free 10 mg/mL and 20 mg/mL nalbuphine HCl solutions for intravenous, intramuscular, and subcutaneous administration makes them medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using nalbuphine HCl and approved drug products containing nalbuphine HCl, there is nothing for FDA to evaluate under question 2.

*N. Polidocanol*

Polidocanol was nominated for inclusion on the 503B Bulks List to compound drug products for the treatment of v[a]ricose and spider veins.[84] The proposed route of administration is intravenous, the proposed dosage form is an injection solution, and the proposed concentration is 1 percent to 5 percent. The nominated bulk drug substance is a component of FDA-approved

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[82] See, e.g., ANDA 070914 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/96944c71-2337-47f2-bab6-f46ad01499f3/96944c71-2337-47f2-bab6-f46ad01499f3.xml.

[83] Per the label for ANDA 070914, single-dose products contain no bacteriostat or antimicrobial agent and unused portions must be discarded.

[84] See Docket No. FDA-2013-N-1524, document no. FDA-2013-N-1524-2292.

drug products. FDA-approved polidocanol (Asclera) is available as a 0.5 percent (5 mg/mL) and 1 percent (10 mg/mL) solution for intravenous administration.[85] In addition, FDA-approved polidocanol (Varithena) is available as a 1 percent (10 mg/mL) solution for intravenous administration that must be activated before use.[86]

1. Suitability of FDA-Approved Drug Product(s)

The nomination proposes polidocanol solution for the 503B Bulks List at a concentration of 1 percent to 5 percent. The nomination does not identify an attribute of the approved products that makes them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. Specifically, the nomination does not explain why the FDA-approved 1 percent solution products are medically unsuitable to treat certain patients for varicose veins or spider veins. While FDA is aware that higher concentrations of polidocanol have sometimes been used to treat patients with larger spider veins and varicose veins, FDA is not aware of patients who would need concentrations above 1 percent for this purpose. Varithena, approved in 2013, demonstrated safety and efficacy based on adequate and well-controlled studies in veins above 12 mm in diameter.

FDA finds no basis to conclude that an attribute of each FDA-approved product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

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[85] See, NDA 021201 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/fe391849-9f70-4c3b-8698-39b243647727/fe391849-9f70-4c3b-8698-39b243647727.xml.

[86] See, NDA 205098 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/5cfae95c-e866-4c37-857c-ab72e7a0fb40/5cfae95c-e866-4c37-857c-ab72e7a0fb40.xml.

Because we are proposing not to include polidocanol on the 503B Bulks list for the reasons described above, we do not consider whether there is a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product.

3. Additional Comments

For the reasons stated above, we did not evaluate this nomination using the factors that we considered for our evaluation in section II.B above. However, we note that polidocanol products that are of higher concentrations than the approved product would deliver higher doses if used in the same volume, potentially posing greater risk to patients.

*O. Potassium Acetate*

Potassium acetate has been nominated for inclusion on the 503B Bulks List to compound drug products that facilitate electrolyte management.[87] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution, and the proposed concentration is 2 milliequivalents per milliliter (mEq/mL). The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of potassium acetate available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that potassium acetate might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug

[87] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

products (e.g., NDA 018896). FDA-approved potassium acetate is available as a 40 mEq/20 mL (2 mEq/mL) preservative-free solution for intravenous administration.[88, 89]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved 2 mEq/mL preservative-free solution products is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using potassium acetate and approved drug products containing potassium acetate, there is nothing for FDA to evaluate under question 2.

*P. Procainamide HCl*

Procainamide HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat ventricular arrhythmia.[90] The proposed routes of administration are intramuscular and intravenous, the proposed dosage form is a preserved solution, and the proposed concentrations are 100 mg/mL and 500 mg/mL. The nominators proposed to compound a preserved solution. However, they failed to acknowledge that there is a preserved formulation of procainamide HCl available that is FDA-approved or explain why that

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[88] See, e.g., NDA 018896 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/fed21ec1-a0e2-457e-9b7d-c9a04f5d8871/fed21ec1-a0e2-457e-9b7d-c9a04f5d8871.xml.

[89] Per the label for NDA 018896, the potassium acetate solution contains no bacteriostat, antimicrobial agent or added buffer but may contain acetic acid for pH adjustment.

[90] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2292 and FDA-2013-N-1524-2298.

formulation would be medically unsuitable for certain patients. The nominations state that procainamide HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 089069). FDA-approved procainamide HCl is available as a 100 mg/mL and 500 mg/mL preserved solution for intramuscular and intravenous administration.[91, 92]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved 100 mg/mL and 500 mg/mL preserved solutions makes them medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because the nominations do not identify specific differences between drug products that would be compounded using procainamide HCl and approved drug products containing procainamide HCl, there is nothing for FDA to evaluate under question 2.

*Q. Sodium Nitroprusside*

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[91] See, e.g., ANDA 089069 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/0ddcc43e-3d9c-4a79-ab19-790d8c0043cd/0ddcc43e-3d9c-4a79-ab19-790d8c0043cd.xml.

[92] Per the label for ANDA 089069, each milliliter of the 2 mL vial contains procainamide hydrochloride 500 mg; methylparaben 1 mg and sodium metabisulfite 1.8 mg added in water for injection and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

Sodium nitroprusside has been nominated for inclusion on the 503B Bulks List to compound drug products to treat acute decompensated heart failure and acute hypertension.[93] The proposed route of administration is a sterile, injectable solution, the proposed dosage form is a diluted injection, and the proposed concentration is 12.5 mg/mL. The nomination states that sodium nitroprusside might also be used to compound other drug products but does not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 209493). FDA-approved sodium nitroprusside is available as a 50 mg/2 mL (25 mg/mL) solution that must be diluted prior to injection.[94, 95]

1. Suitability of FDA-Approved Drug Product(s)

The nomination does not explain why an attribute of each of the FDA-approved 50 mg/2 mL solution for dilution products are medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug product is intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

The nomination does not take the position or provide support for the position that drug products containing sodium nitroprusside must be compounded from bulk drug substances rather than using the approved drug product. FDA finds no basis to conclude that the sodium

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[93] See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0238.
[94] See, e.g., ANDA 209493 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/61245426-5d5a-4788-b060-33671152b526/61245426-5d5a-4788-b060-33671152b526.xml.
[95] Sodium nitroprusside is also approved as a solution for intravenous administration.

nitroprusside drug products proposed in the nomination must be compounded using a bulk drug substance rather than using the approved drug product.

*R. Sodium Thiosulfate*

Sodium thiosulfate has been nominated for inclusion on the 503B Bulks List for the treatment of calciphylaxis, cyanide toxicity, extravasation, *Malassezia furfur*, and nephrotoxicity prophylaxis.[96] Sodium thiosulfate was nominated as a 250 mg/mL injectable, for intravenous, intradermal, intramuscular, and subcutaneous administration, and in a topical dosage form at an unknown concentration. The nominated bulk drug substance is a component of an FDA-approved drug product (NDA 203923). FDA-approved sodium thiosulfate is available as a 12.5 g/50 mL (250 mg/mL) solution for intravenous administration.[97, 98]

1. Suitability of FDA-Approved Drug Product(s)

Sodium thiosulfate was nominated for injectable (intravenous, intradermal, intramuscular, subcutaneous) and topical administration[99] for the treatment of calciphylaxis, cyanide toxicity, extravasation, *Malassezia furfur*, and nephrotoxicity prophylaxis.

a. Calciphylaxis.

The nominator proposes to remove potassium chloride from the proposed injectable compounded product used in the treatment of calciphylaxis. The nominator asserts that the safety of the approved product is of concern because the potassium level of the product is too

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[96] See Docket No. FDA-2015-N-3469, document no. FDA-2015-N-3469-0173.
[97] See, e.g., NDA 203923 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/29449d76-f4c7-4571-b7bb-5c2a55f637b5/29449d76-f4c7-4571-b7bb-5c2a55f637b5.xml.
[98] Sodium thiosulfate is also approved for sequential use with sodium nitrite for intravenous administration.
[99] The topical route of administration will not be considered further because the nomination does not identify a condition that this formulation is intended to address. The nomination also did not identify an attribute of the approved intravenous drug product that makes it medically unsuitable to treat patients with the conditions for which the bulk drug substance was nominated.

high for patients with renal disease or impairment. This assertion is inaccurate because the amount of potassium in the approved 12.5 g/50 mL (250 mg/mL) solution for intravenous administration is small (440 mg or ~ 6 mEq potassium chloride per dose), and when it is used off-label for the treatment of calciphylaxis, to the best of our knowledge, the product is generally administered during hemodialysis, which allows for removal of the excess potassium.[100]

The nomination proposes to make a 250 mg/mL injectable, as well as unspecified higher concentrations. The nomination states that it may be necessary to compound a product with a greater concentration than is commercially available, but the nomination does not identify specific higher concentrations that the nominator proposes to compound or provide any data or information supporting the need for a higher concentration. In addition, FDA is not aware of patients who would need concentrations above 250 mg/mL. The approved product is available as a concentrated solution (12.5 g/50 mL). Although the product is generally diluted in normal saline before administration to minimize potential complications associated with the intravenous infusion of a hypertonic solution, presumably, a concentrated, compounded sodium thiosulfate product would also need to be diluted before administration. In addition, when used for the treatment of calciphylaxis in hemodialysis patients, the product is administered during dialysis, which allows for removal of excess fluid (Refs. 9 to 11) (discussing how sodium thiosulfate is generally used to treat calciphylaxis).

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[100] Even in circumstances where it is not administered during dialysis, the amount of potassium in the approved product is small and potassium levels could be monitored for safety. (See, e.g. Nigwekar, S.U., S.M. Brunelli, D. Meade, et al., 2013, "Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy, " *Clinical Journal of the American Society of Nephrology*, 8(7):1162-1170 (providing, "The median dose of STS treatment was 25 g administered intravenously in 100 ml of normal saline given over the last half-hour of each HD session"); Generali, J.A. and D.J. Cada, 2015, "Sodium Thiosulfate: Calciphylaxis," *Hospital Pharmacy*, 50(11):975-977 (studying dialysis patients on "25 grams intravenously diluted in 100 mL of sodium chloride 0.9 percent administered over 30 to 60 minutes 3 times per week during the last hour or after the hemodialysis session."))

Accordingly, FDA finds no basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable to treat patients with calciphylaxis and that the sodium thiosulfate drug products proposed to be compounded are intended to address.[101]

b. Cyanide toxicity.

The nomination also proposes to combine sodium thiosulfate with sodium nitroprusside to reduce the risk of cyanide toxicity during sodium nitroprusside administration. Sodium thiosulfate is FDA-approved for sequential use with sodium nitrite for treatment of acute cyanide poisoning that is judged to be serious or life-threatening. The nomination states that sodium thiosulfate is commonly administered with sodium nitroprusside, but the nomination does not identify the final product formulation proposed to be compounded (e.g. dosage form and strength of each ingredient).[102] Sodium nitroprusside was also nominated separately (see FDA's analysis at section IV.Q. above), but that nomination does not mention the use of sodium nitroprusside in combination with sodium thiosulfate.

The nomination states that providing sodium thiosulfate and sodium nitroprusside in a combined compounded preparation would allow for faster administration in the clinical setting and fewer human manipulations, thus reducing the rate of error. We do not consider the risk that

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[101] In making this observation, we do not suggest that the approved drug product, or products prepared from it, are approved for the use proposed by the nomination. Here we are asking a limited, threshold question to determine whether there might be clinical need for a compounded drug product, by asking what attributes of the approved drug the proposed compounded drug would change, and why. Asking this question helps ensure that if a bulk drug substance is included on the 503B Bulks List it is to compound drugs that include a needed change to an approved drug product rather than to produce drugs without such a change. Because our answer to question (1) is "no", we do not evaluate the available evidence of effectiveness or lack of effectiveness of a drug product compounded with sodium thiosulfate for the treatment of calciphylaxis. We note that the references cited by the nominator appear to be general reviews of potassium homeostasis and studies in other populations showing associations between potassium excretion or potassium levels and clinical outcomes. None of these references address whether there is a risk of the amount of potassium in the approved product to patients receiving sodium thiosulfate for the treatment of calciphylaxis.

[102] While the nomination does not provide final product formulation information, it does include an article (Ref. 12), which reports on the stability of a 1:10 sodium nitroprusside: sodium thiosulfate admixture stored up to 48 hours when compounded from the approved products.

a clinician may mishandle the approved product to be an indicator of clinical need. Further, the approved labeling for sodium nitroprusside states that no other drugs should be administered in the same solution with sodium nitroprusside. The nomination has not identified any patients for whom co-administration of both approved drug products would not be medically appropriate, and for whom compounding a drug product with both active ingredients in one solution would address an unmet medical need.

Accordingly, with respect to the combination sodium thiosulfate and sodium nitroprusside drug products proposed to be compounded, FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients.

c. Extravasation, *Malassezia furfur*, and nephrotoxicity prophylaxis.

The nomination does not identify an attribute of the approved products that makes them medically unsuitable for the conditions listed above and that the proposed compounded injectable drug products are intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

Because we are proposing not to include sodium thiosulfate on the 503B Bulks list for the reasons described above, we do not consider whether there is a basis to conclude that the drug products proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product.

*S. Verapamil HCl*

Verapamil HCl has been nominated for inclusion on the 503B Bulks List to compound drug products that treat atrial fibrillation and flutter, hypertension, and paroxysmal

supraventricular tachycardia, among other conditions.[103] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution, and the proposed concentration is 2.5 mg/mL. The nominators proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of verapamil HCl available that is FDA-approved or explain why that formulation would be medically unsuitable for certain patients. The nominations state that verapamil HCl might also be used to compound other drug products but do not identify those products. The nominated bulk drug substance is a component of FDA-approved drug products (e.g., ANDA 070737). FDA-approved verapamil HCl is available as a preservative-free 5 mg/2 mL (2.5 mg/mL) solution for intravenous administration.[104, 105, 106]

1. Suitability of FDA-Approved Drug Product(s)

The nominations do not explain why an attribute of each of the FDA-approved preservative-free 5 mg/2 mL (2.5 mg/mL) solution products for intravenous administration is medically unsuitable for certain patients or identify an attribute of the approved drug products that the proposed compounded drug products are intended to address. FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation and that a proposed compounded product is intended to address.

2. Whether the Drug Product Must be Compounded from a Bulk Drug Substance

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[103] See Docket No. FDA-2013-N-1524, document nos. FDA-2013-N-1524-2298 and FDA-2013-N-1524-2292.
[104] See, e.g., ANDA 070737 labeling available as of the date of this notice at https://www.accessdata.fda.gov/spl/data/3d8f6e3e-444b-44e3-b60c-a725948085b6/3d8f6e3e-444b-44e3-b60c-a725948085b6.xml.
[105] Per the label for ANDA 070737, the solution contains no bacteriostat or antimicrobial agent and is intended for single-dose intravenous administration and may contain hydrochloric acid for pH adjustment.
[106] Verapamil hydrochloride is also approved as oral extended release tablet.

Because the nominations do not identify specific differences between drug products that would be compounded using verapamil HCl and approved drug products containing verapamil HCl, there is nothing for FDA to evaluate under question 2.

## V. Other Issues Raised in Nominations

Some of the bulk drug substance nominations included in this notice state that there could be a benefit gained from using a bulk drug substance contained in an approved drug product to compound drug products that do not require dilution or reconstitution prior to administration. As explained above, when a bulk drug substance is a component of an approved drug, we considered whether there is a basis to conclude that an attribute of each approved drug product makes each one medically unsuitable to treat certain patients for their condition, an interpretation that protects patients and the integrity of the drug approval process. The nominations proposing to compound drug products in ready-to-use form containing bulk drug substances in one or more FDA-approved drug products do not show that the approved drug product, when not manufactured in the ready-to-use form, is medically unsuitable for certain patients. Nor do the nominations establish that drug products in the relevant concentrations, including ready-to-use products, cannot be prepared from the approved drug products. Rather, they propose to compound a ready-to-use product from bulk drug substances to seek improved efficiency for prescribers or healthcare providers, or to address the possibility that the approved drug might be mishandled by a medical professional, neither of which falls within the meaning of clinical need to compound a drug product using a bulk drug substance.

Some of the nominations for the substances in this notice include statements that these substances should be added to the 503B Bulks List because compounding from the bulk drug substance could help outsourcing facilities address drug shortages and supply disruptions of

approved drugs. As noted above, section 503B of the FD&C Act contains a separate provision for compounding from bulk drug substances to address a drug shortage, and we do not interpret the other price- and supply-related issues advanced by the nominations to be within the meaning of "clinical need" for compounding with a bulk drug substance.[107]

Some of the nominations for the substances in this notice assert that it would be preferable to compound a drug product using a bulk drug substance rather than using an approved drug product; however, they do not take the position or provide support for the position that a bulk drug substance must be used to prepare these concentrations.[108]

## VI. Conclusion

For the reasons stated above, we tentatively conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances DPCP, glycolic acid, SADBE, and TCA, and we therefore propose to include them on the 503B Bulks List as described in this notice.

At this time, we find no basis to conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, sodium

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[107] Please see the final guidance entitled "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act" (84 FR 7390) (Ref. 2) and the *Federal Register* notice entitled "List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act" available at https://www.federalregister.gov/documents/2019/03/04/2019-03810/list-of-bulk-drug-substances-for-which-there-is-a-clinical-need-under-section-503b-of-the-federal.

[108] For example, the nominations do not take the position or provide support for the position that a drug product prepared by starting with the approved drug would be unsuitable for administration.

thiosulfate, and verapamil HCl. We therefore propose not to include these bulk drug substances on the 503B Bulks List.

## VII. 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 are also available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. 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. FDA, Guidance for Industry, "Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act," January 2017 (available at https://www.fda.gov/media/94402/download).

*2. FDA, Guidance for Industry, "Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act," March 2019 (available at https://www.fda.gov/media/121315/download).

*3. FDA Memorandum to File, Clinical Need for Diphenylcyclopropenone (DPCP) in Compounding Under Section 503B of the FD&C Act, July 2020.

*4. FDA Memorandum to File, Clinical Need for Glycolic Acid in Compounding Under Section 503B of the FD&C Act, July 2020.

*5. FDA Memorandum to File, Clinical Need for Squaric Acid Dibutyl Ester (SADBE) in Compounding Under Section 503B of the FD&C Act, July 2020.

*6. FDA Memorandum to File, Clinical Need for Trichloroacetic Acid (TCA) in Compounding Under Section 503B of the FD&C Act, July 2020.

7. Leheta, T. M., A. El Tawdy, R. M. Abdel Hay, and S. Farid, 2011, "Percutaneous Collagen Induction Versus Full-Concentration Trichloroacetic Acid in the Treatment of Atrophic Acne Scars," *Dermatologic Surgery*, 37(2):207-216.

8. Kumari, R. and D. M. Thappa, 2010, "Comparative Study of Trichloroacetic Acid Versus Glycolic Acid Chemical Peels in the Treatment of Melasma," *Indian Journal of Dermatology, Venereology and Leprology*, 76:447, available at http://www.ijdvl.com/text.asp?2010/76/4/447/66602.

9. Nigwekar, S. U., S. M. Brunelli, D. Meade, et al., 2013, "Sodium Thiosulfate Therapy for Calcific Uremic Arteriolopathy," *Clinical Journal of the American Society of Nephrology*, 8(7):1162-1170.

10. Generali, J. A. and D. J. Cada, 2015, "Sodium Thiosulfate: Calciphylaxis," *Hospital Pharmacy*, 50(11):975-977.

*11. Udomkarnjananun, S., K. Kongnatthasate, K. Praditpornsilpa, et al., 2019, "Treatment of Calciphylaxis in CKD: A Systematic Review and Meta-Analysis," *Kidney International Reports*, 4(2):231-244.

*12. Schulz, L. T., E. J. Elder, Jr, K.J. Jones, et al., 2010, "Stability of Sodium Nitroprusside and Sodium Thiosulfate 1:10 Intravenous Admixture," *Hospital Pharmacy*, 45(10):779-784.

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