Title: Red Flags Rule, 16 CFR 681.1; Card Issuers Rule, 16 CFR 681.2; Address Discrepancy Rule, 16 CFR part 641.

OMB Control Number: 3084–0137.

Type of Review: Extension of currently approved collection.

Abstract: The Red Flags Rule requires financial institutions and certain creditors to develop and implement written Identity Theft Prevention Programs. The Card Issuers Rule requires credit and debit card issuers to assess the validity of notifications of address changes under certain circumstances. The Address Discrepancy Rule provides guidance on what covered users of consumer reports must do when they receive a notice of address discrepancy from a nationwide consumer reporting agency. Collectively, these three anti-identity theft provisions are intended to prevent impostors from misusing another person's personal information for a fraudulent purpose.

The Rules implement sections 114 and 315 of the Fair Credit Reporting Act (''FCRA''), 15 U.S.C. 1681 *et seq.*

Estimated Annual Burden: (397,298 hours; $20,103,752 in labor costs).

A. Section 114: Red Flags and Card Issuers Rules:
   (1) Red Flags:
   (a) *Estimated Number of Respondents:* 164,591
   (i) *High-Risk Entities:* 99,830 [1]
   (ii) *Low-Risk Entities:* 64,761 [2]
   (b) *Estimated Hours Burden:*
   (i) *High-Risk Entities:* 342,900 hours
   (ii) *Low-Risk Entities:* 16,523 hours
   (2) Card Issuers Rule:
   (a) *Estimated Number of Respondents:* 18,894 [3]
   (b) *Estimated Hours Burden:* 20,508 hours
   (3) *Combined Labor Cost Burden:* $19,756,412

B. Section 315—Address Discrepancy Rule:
   (1) *Estimated Number of Respondents:* 44,000
   (2) *Estimated Hours Burden:* 17,367 hours
   (3) *Estimated Labor Cost Burden:* $347,340

C. Capital/Non-Labor Costs for Sections 114 and 315

FTC staff believes that the Rules impose negligible capital or other non-labor costs, as the affected entities are likely to have the necessary supplies and/or equipment already (*e.g.,* offices and computers) for the information collections described herein.

Request for Comment

On October 15, 2021, the FTC sought public comment on the information collection requirements associated with the Rule. 86 FR 57425. The Commission received no germane comments. Pursuant to the OMB regulations, 5 CFR part 1320, that implement the PRA, 44 U.S.C. 3501 *et seq.,* the FTC is providing this second opportunity for public comment while seeking OMB approval to renew the pre-existing clearance for the Rules.

Your comment—including your name and your state—will be placed on the public record of this proceeding. Because your comment will be made public, you are solely responsible for making sure that your comment does not include any sensitive personal information, such as anyone's Social Security number; date of birth; driver's license number or other state identification number, or foreign country equivalent; passport number; financial account number; or credit or debit card number. You are also solely responsible for making sure that your comment does not include any sensitive health information, such as medical records or other individually identifiable health information. In addition, your comment should not include any ''trade secret or any commercial or financial information which . . . is privileged or confidential'' —as provided by Section 6(f) of the FTC Act, 15 U.S.C. 46(f), and FTC Rule 4.10(a)(2), 16 CFR 4.10(a)(2)—including in particular competitively sensitive information such as costs, sales statistics, inventories, formulas, patterns, devices, manufacturing processes, or customer names.

Josephine Liu,

Assistant General Counsel for Legal Counsel.

[FR Doc. 2022–01539 Filed 1–26–22; 8:45 am]

BILLING CODE 6750–01–P

[1] High-risk entities include, for example, financial institutions within the FTC's jurisdiction and utilities, motor vehicle dealerships, telecommunications firms, colleges and universities, and hospitals.

[2] Low-risk entities include, for example, public warehouse and storage firms, nursing and residential care facilities, automotive equipment rental and leasing firms, office supplies and stationery stores, fuel dealers, and financial transaction processing firms.

[3] FTC staff estimates that the Rule affects as many as 18,356 card issuers within the FTC's jurisdiction. This includes, for example, state credit unions, general retail merchandise stores, colleges and universities, and telecoms.

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, the Agency or we) is evaluating substances that have been nominated for inclusion on a list of bulk drug substances (*i.e.,* 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 is including on the list at this time: Diphenylcyclopropenone (DPCP) for topical use only, glycolic acid for topical use only in concentrations up to 70 percent, squaric acid dibutyl ester (SADBE) for topical use only, and trichloroacetic acid (TCA) for topical use only. This notice also identifies eight bulk drug substances that FDA has considered and is not including on the list at this time: diazepam, dipyridamole, dobutamine hydrochloride (HCl), dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, and sodium thiosulfate (except for topical administration). Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and will be the subject of future notices.

DATES: The announcement of the notice is published in the **Federal Register** on January 27, 2022.

ADDRESSES: For access to the docket to read background documents or comments received, go to *https://www.regulations.gov* and insert the docket number found in brackets in the heading of this notice 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: Kemi Asante, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New

Hampshire Ave., Bldg. 51, Rm. 2247, Silver Spring, MD 20993, 301–796–3110.

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 in 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 of the FD&C Act (21 U.S.C. 360eee–1) (concerning drug supply chain security requirements).[1]

Compounded drug products 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, 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 the 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 (the Secretary) identifying bulk drug substances for which there is a clinical need (the 503B Bulks List) or (2) the drug compounded from the bulk drug substance 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]

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]

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]

FDA has published a series of **Federal Register** notices addressing bulk drug substances nominated for inclusion on the 503B Bulks List.[10] This notice identifies four bulk drug substances that FDA has considered and is including on the 503B Bulks List and eight bulk drug substances that FDA has considered and is not including on the 503B Bulks List.

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. In the **Federal Register** of 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, renominate substances with sufficient information, or submit comments on nominated substances.

As FDA evaluates bulk drug substances, it intends to publish notices for public comment in the **Federal Register** that describe its proposed position on each substance along with the rationale for that position.[11] 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.[12] 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. FDA will then publish in the **Federal Register** a final determination 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 final determination regarding 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 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. This list is available at *https://www.fda.gov/media/120692/download.* FDA will only place a bulk drug substance on the 503B Bulks List when it has determined there

[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.

[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 United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists.

[10] See **Federal Register** of August 28, 2018 (83 FR 43877), March 4, 2019 (84 FR 7383), September 3, 2019 (84 FR 46014), July 31, 2020 (85 FR 46126), and March 24, 2021 (86 FR 15673). The comment period for the July 2020 notice was reopened for 30 days on January 8, 2021 (86 FR 1515), to allow interested parties an additional opportunity to comment. In this notice, FDA is reaching a final determination on whether certain substances evaluated in the September 2019 and July 2020 notices will be included on the 503B Bulks List. The substances considered in the September 2019 and July 2020 notices that are not addressed in this notice remain under consideration by the Agency. In addition, bumetanide, which was considered in the August 2018 notice remains under consideration by the Agency.

[11] This is consistent with procedures 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.

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

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 is evaluating 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).[13]

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 evaluating bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the standard provided by the statute (Ref. 2).[14] In applying this standard to make determinations regarding the substances set forth 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 of the FD&C Act 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 when assessing ''clinical need.''

Eight of the bulk drug substances that we are addressing in this notice are components of FDA-approved drug products,[15] and we evaluated them by asking one or both of the following questions:

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 to be 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. When it is feasible to compound a drug product by starting with an approved drug product, there are certain benefits of doing so over starting with a bulk drug substance, including that approved drugs have undergone premarket review for safety, effectiveness, and quality, and are manufactured by a facility that is subject to premarket assessment, including site inspection, as well as routine post-approval risk-based inspections. In contrast, FDA does not conduct a premarket review of the quality standards, specifications, and controls for bulk drug substances used in compounding and does not conduct a premarket assessment of the manufacturer of the bulk drug substance.

If the answer to both of the above 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 eight 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 have decided 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, DPCP, glycolic acid, SADBE, and TCA, we conducted a balancing test with four factors, considered each factor in the context of the others, and balanced them to determine whether the statutory ''clinical need'' standard was met. The balancing test includes the following factors:

- The physical and chemical characterization 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, if any such evidence exists; and
- 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

[13] In January 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'' (the ''Interim Policy''), available at *https://www.fda.gov/media/94402/download.*

[14] In March 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'' (the ''Clinical Need Guidance''), 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. The analysis under the statutory ''clinical need'' standard described in this notice is consistent with the approach described in FDA's guidance.

[15] Specifically, diazepam, dipyridamole, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, and sodium thiosulfate.

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 decision to include four bulk drug substances on the 503B Bulks List.

C. Inclusion of a Bulk Drug Substance on the 503B Bulks List or Exclusion From the List

In evaluating a substance for the 503B Bulks List, FDA considered whether the clinical need for the bulk drug substance in the compounded drug product is limited, by, for example, route of administration or dosage form. As appropriate, and as explained further below, the Agency tailored its entries on the 503B Bulks List to reflect its findings related to clinical need for these bulk substances. Specifically, the listings for DCPC, glycolic acid, SADBE, and TCA are limited to the use of these bulk drug substances to compound drug products for topical use only.

In the **Federal Register** notice of July 31, 2020, which proposed updates to the 503B Bulks List, FDA solicited comment on whether: (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 (85 FR 46126). FDA received a comment supporting the first option and stating that ''FDA should restrict the use of any bulk drug substance on the 503B Bulks List in combination with one or more other active ingredients, unless there is specific clinical need for the combination product, as determined through FDA evaluation.'' In addition, the comment stated that this approach is important to limit safety risks to patients, particularly given the higher complexity of combination formulations.

FDA has determined that to be eligible for the statutory exemptions under section 503B, drug products compounded using a bulk drug substance that appears on the 503B Bulks List cannot contain other active pharmaceutical ingredients unless those active pharmaceutical ingredients have been listed in combination on the 503B Bulks List. FDA's assessment of the clinical need for compounding with a particular bulk drug substance or combination of bulk drug substances could be affected if a bulk drug substance is commonly used in compounded drug products that contain multiple bulk drug substances (active pharmaceutical ingredients). The use of certain active pharmaceutical ingredients in combination with other active pharmaceutical ingredients in a compounded drug product could also pose a safety risk or affect the compounded drug product's effectiveness. These considerations of the composition of a nominated compounded combination, the history of its use in compounding, and evidence of safety or effectiveness would be included in FDA's clinical need evaluation.

III. FDA's Determinations Regarding Substances Proposed for the 503B Bulks List

In September 2019, the Agency issued a **Federal Register** notice in which it evaluated nine nominated bulk drug substances under the section 503B statutory standard—dipyridamole, ephedrine sulfate, famotidine, hydralazine HCl, methacholine chloride, sodium bicarbonate, sodium tetradecyl sulfate, trypan blue, and vecuronium bromide—and proposed not to include them on the 503B Bulks List (the September 2019 notice).[16] In this notice, after review of the comments submitted to the docket for the September 2019 notice, FDA is making its final determination with regard to dipyridamole. At this time, FDA is not making a final determination regarding ephedrine sulfate, famotidine, hydralazine HCl, methacholine chloride, sodium bicarbonate, sodium tetradecyl sulfate, trypan blue, and vecuronium bromide. These substances remain under consideration by FDA.

In July 2020, the Agency issued a **Federal Register** notice in which it evaluated 23 nominated bulk drug substances under the section 503B statutory standard (the July 2020 notice).[17] FDA proposed to include DPCP, glycolic acid, SADBE, and TCA on the 503B Bulks List. FDA proposed not to include 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 on the 503B Bulks List. In this notice, after review of the comments submitted to the docket for the July 2020 notice, FDA is making its final determination for DPCP, glycolic acid, SADBE, TCA, diazepam, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, and sodium thiosulfate. At this time, FDA is not making a final determination regarding hydroxyzine HCl, ketorolac tromethamine, labetalol HCl, mannitol, metoclopramide HCl, moxifloxacin HCl, nalbuphine HCl, polidocanol, potassium acetate, procainamide HCl, sodium nitroprusside, and verapamil HCl. These substances remain under consideration by FDA. 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.

A. Substances Evaluated and Included on the 503B Bulks List

Because the substances in this section are not components of FDA-approved drug products, FDA applied the balancing test described above. The four bulk drug substances that FDA evaluated, proposed to include on the 503B Bulks List in a July 2020 **Federal Register** notice, and is now placing on the 503B Bulks List are: DPCP, glycolic acid, SADBE, and TCA. The reasons for FDA's proposals are included below (Refs. 3–6).[18] Having received no adverse comment, and for the same reasons set forth in those proposals, FDA is now placing these four bulk drug substances on the 503B Bulks List.

1. 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.[19] 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

[16] See 84 FR 46014.

[17] See 85 FR 46126.

[18] As explained in the July notice, 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) in addition to the nominations for the 50B Bulks List. 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.

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

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 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. No commenters disagreed with FDA's proposal to include DPCP for topical use only on the 503B Bulks List. Accordingly, we are adding DPCP to the 503B Bulks List for topical use only.

2. 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.[20] 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 of the FD&C Act, 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 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. No commenters disagreed with FDA's proposal to include glycolic acid on the 503B Bulks List. Accordingly, we are adding glycolic acid to the 503B Bulks List for topical use only in concentrations up to 70 percent.

3. 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.[21] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated SADBE 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 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 of 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. No commenters disagreed with FDA's proposal to include SADBE on the 503B Bulks List. Accordingly, we are adding SADBE to the 503B Bulks List for topical use only.

4. 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.[22] 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 of the FD&C Act, considering data and information regarding the physical and chemical characterization of TCA, safety

[20] 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 in this notice does not consider whether there is a clinical need for outsourcing facilities to compound drug products containing glycolic acid and hydroquinone or tretinoin, or other bulk drug substances, which may be the subject of future **Federal Register** notices.

[21] See Docket No. FDA–2013–N–1524, document no. FDA–2013–N–1524–1363.

[22] See Docket No. FDA–2018–D–1067, document no. FDA–2018–D–1067–0005.

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 List. No commenters disagreed with FDA's proposal to include TCA on the 503B Bulks List. Accordingly, we are adding TCA to the 503B Bulks List for topical use only.

B. Substances Evaluated and Not Included on the 503B Bulks List

Because the substances in this section are components of FDA-approved drug products, FDA considered one or both of the following questions: (1) Is there 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 eight bulk drug substances that FDA has evaluated, proposed not to include on the 503B Bulks List in a **Federal Register** notice, and has now decided not to place on the 503B Bulks List are: Diazepam, dipyridamole, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, and sodium thiosulfate (except for topical administration).

1. Diazepam

Diazepam was 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.[23] The proposed route of administration is intravenous or intramuscular, the proposed dosage form is a preserved 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.[24] [25] [26]

a. 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.

Two commenters agreed with FDA's proposal not to include diazepam on the 503B Bulks List. Several commenters objected generally to FDA's proposals in the July 2020 notice and these overarching concerns are addressed in section IV. No new information supporting the clinical need for compounding from the bulk drug substance diazepam was provided by the commenters.

Accordingly, 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.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

The nominations do not identify specific differences between drug products that would be compounded using diazepam and approved drug products containing diazepam, and no further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance.

2. Dipyridamole

Dipyridamole was nominated for inclusion on the 503B Bulks List to compound drug products that are used for thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.[27] The proposed route of administration is intravenous, the proposed dosage form is an injection, and the proposed strength is 1 milligram per milliliter (mg/mL) in a 50 mL and 60 mL syringe. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* ANDAs 074521 and 074939). FDA-approved dipyridamole is available as a 5 mg/mL injection for intravenous administration.[28] [29] Per its labeling, it should be diluted to a final concentration of less than or equal to 2.5 mg/mL.[30]

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

[24] 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.*

[25] 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.

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

[27] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0031.

[28] See, *e.g.,* ANDA 074521 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/baa2cb6d-2b97-4ad3-a5fc-bad3b8bc6175/baa2cb6d-2b97-4ad3-a5fc-bad3b8bc6175.xml.*

[29] Dipyridamole is also approved as an oral tablet and in combination with aspirin as an extended release capsule.

[30] According to the label for ANDA 074521, dipyridamole injection should be diluted in at least a 1:2 ratio with sodium chloride injection 0.45%, sodium chloride injection 0.9% or dextrose injection 5% for a total volume of approximately 20 to 50 mL.

a. Suitability of FDA-Approved Drug Product

The nomination does not identify an attribute of the FDA-approved drug 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 5 mg/mL injection (for dilution) is medically unsuitable for certain patients.

Several commenters agreed with FDA's proposal not to include dipyridamole on the 503B Bulks List. One commenter objected generally to FDA's proposals in the September 2019 notice asserting that FDA was inappropriately engaging in the practice of medicine. This overarching concern is addressed in section IV. No new information supporting the clinical need for compounding from the bulk drug substance dipyridamole was provided by commenters. Accordingly, 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.

b. 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 dipyridamole must be compounded from bulk drug substances rather than by diluting the approved drug product, and no further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the dipyridamole drug products proposed in the nominations must be compounded using a bulk drug substance rather than an approved drug product.

3. Dobutamine HCl

Dobutamine HCl was 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.[31] The proposed route of administration is intravenous, 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 intravenous 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 HCl drug products as equivalent (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 (no further dilution needed) for intravenous administration and as an EQ 12.5mg base/mL single-dose vial that must be diluted prior to infusion.[32] [33]

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

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.

Two commenters agreed with FDA's proposal not to include dobutamine HCl on the 503B Bulks List. Several commenters objected generally to FDA's proposals in the July 2020 notice and these overarching concerns are addressed in section IV. No new information supporting the clinical need for compounding from the bulk drug substance dobutamine HCl was provided by the commenters.

Accordingly, 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.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

The nomination does not identify specific differences between drug products that would be compounded using dobutamine HCl and approved drug products containing dobutamine HCl, and no further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance.

4. 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.[34] 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 did not 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 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.[35] [36]

a. 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.

Two commenters agreed with FDA's proposal not to include dopamine HCl on the 503B Bulks List. Several commenters objected generally to FDA's proposals in the July 2020 notice and these overarching concerns are

[31] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0032.

[32] 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.*

[33] 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.*

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

[35] 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.*

[36] 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.

addressed in section IV. No new information supporting the clinical need for compounding from the bulk drug substance dopamine HCl was provided by the commenters.

Accordingly, 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.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

The nominations do not identify specific differences between drug products that would be compounded using dopamine HCl and approved drug products containing dopamine HCl, and no further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance.

5. Edetate Calcium Disodium

Edetate calcium disodium dihydrate was 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.[37] The proposed route of administration is slow intravenous, the proposed dosage form is a preservative-free injection, and the proposed concentration is 200 mg/mL. The nominators proposed to compound a preservative-free solution. However, they did not 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).[38] FDA-approved edetate calcium disodium is available as a preservative-free 200 mg/mL injection for intravenous and intramuscular administration.[39] [40]

a. 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.

Several commenters on FDA's proposal not to include edetate calcium disodium on the 503B Bulks List assert that there is a clinical need for a compounded drug product containing edetate calcium disodium for intravenous administration for heavy metal chelation and conditions including coronary artery disease, neuropathy, and memory loss. However, the commenters do not explain why an attribute of the FDA-approved product 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.

Several commenters also claimed that FDA erroneously stated that edetate calcium disodium was available as an FDA-approved product in the July 2020 notice when the product was discontinued and is not available in manufactured form. FDA disagrees with these comments. FDA correctly identified the nominated bulk drug substance as a component of an FDA-approved drug product (NDA 008922), which is a preservative-free 200 mg/mL injection for intravenous and intramuscular administration.[41] Although a 500 mg tablet containing edetate calcium was approved under the same NDA number and was discontinued, this has no bearing on the availability of the currently marketed approved formulation for injection.[42] The fact that the 500 mg tablet is no longer marketed does not affect our evaluation of the nomination for edetate calcium disodium because there is a currently-marketed FDA-approved drug product for injection that contains edetate calcium disodium, and the nominators proposed to compound a drug product for injection. Other commenters agreed with FDA's proposal not to include edetate calcium disodium on the 503B Bulks List.

As described above, no new information supporting the clinical need for compounding from the bulk drug substance edetate calcium disodium was provided by the commenters. Taking into consideration the comments submitted and FDA's clinical need analysis, FDA finds no basis to conclude that an attribute of the approved drug 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.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

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, and no further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance.

6. Folic Acid

Folic acid was nominated for inclusion on the 503B Bulks List to compound drug products that treat megaloblastic and macrocytic anemias.[43] 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.[44] [45]

a. 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

[37] 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.

[38] 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.

[39] 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.*

[40] 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.

[41] See fn. 40.

[42] See drug products on NDA 008922 available at *https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=008922.*

[43] See Docket No. FDA–2013–N–1524, document no. FDA–2013–N–1524–2292.

[44] 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.*

[45] Folic acid is also approved as a single-active-ingredient, oral tablet.

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.

Two commenters agreed with FDA's proposal not to include folic acid on the 503B Bulks List. Several commenters objected generally to FDA's proposals in the July 2020 notice and these overarching concerns are addressed in section IV. No new information supporting the clinical need for compounding from the bulk drug substance folic acid was provided by the commenters.

Accordingly, 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.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

The nomination does not identify specific differences between drug products that would be compounded using folic acid and approved drug products containing folic acid, and no further information was supplied on this point during the comment period. Therefore, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance.

7. Glycopyrrolate

Glycopyrrolate bromide was 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. 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 did not 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 mL preserved and preservative-free, single-dose vials for intramuscular or intravenous administration.[46] [47] [48]

a. 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. Two commenters agreed with FDA's proposal not to include glycopyrrolate on the 503B Bulks List. No new information supporting the clinical need for compounding from the bulk drug substance glycopyrrolate was provided by the commenters.

Accordingly, 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.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

The nominations do not identify specific differences between drug products that would be compounded using glycopyrrolate and approved drug products containing glycopyrrolate.

One commenter submitted arguments regarding the need for compounding from the bulk drug substance. The commenter stated that outsourcing facilities supply a substantial portion of the market for glycopyrrolate injectable products and not including glycopyrrolate on the 503B Bulks List will remove substantial volume from the market and may create a shortage for that product. In addition, the commenter stated that glycopyrrolate products compounded from bulk drug substances are ready-to-use, an attribute that is essential for a medication used in emergency situations, and are a safer alternative to commercially available drug products. The commenter also stated that the additional manipulations required to compound a drug product using the FDA-approved finished product as a starting material would be costly in both labor and time.

FDA disagrees with this comment. Regarding the comment's concern about a shortage, as noted above, section 503B(a)(2)(A) of the FD&C Act allows compounding from bulk drug substances if the drug product compounded from such bulk drug substance is on the drug shortage list in effect under section 506E of the FD&C Act at the time of compounding, distribution, and dispensing. The Agency does not interpret supply issues, such as shortages and backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance.[49]

Regarding the concern about ready-to-use drug products, the comment does not establish that drug products, including ready-to-use products, cannot be prepared from the approved glycopyrrolate drug products. Rather, the commenter proposes to compound ready-to-use products from bulk drug substances to seek improved efficiency for prescribers or healthcare providers and 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.

Regarding the concern about starting from an FDA-approved drug product, FDA does not interpret considerations of cost to be within the meaning of ''clinical need.'' Allowing outsourcing facilities to compound a drug product from a bulk drug substance that is a component of an FDA-approved drug product because of economic incentives, when the approved drug product, or a drug product compounded from the approved drug product, would be medically appropriate for the patient, would undermine the incentive for applicants to seek FDA approval of drug products.

Having considered these arguments, and because and no further information

[46] 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.*

[47] 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.

[48] Glycopyrrolate is also approved as an oral tablet, oral solution, and for inhalation as a single-active-ingredient product.

[49] 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 March 2019 **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'' (84 FR 7383).

was supplied regarding the clinical need for compounding from the bulk drug substance, FDA finds no basis to conclude that the drug product proposed to be compounded must be prepared using a bulk drug substance.

8. Sodium Thiosulfate

Sodium thiosulfate was nominated for inclusion on the 503B Bulks List for the treatment of calciphylaxis, cyanide toxicity, extravasation, *Malassezia furfur,* and nephrotoxicity prophylaxis.[50] 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. FDA intends to address the topical route of administration in a future **Federal Register** notice because a comment provided additional support for FDA to evaluate it. FDA is not making a decision on sodium thiosulfate for topical administration at this time and compounded drug products that contain sodium thiosulfate for topical administration may be eligible for the enforcement discretion policy described in FDA's Interim Policy provided the circumstances described in the guidance are present. FDA's evaluation here addresses the clinical need for a compounded sodium thiosulfate drug product except for topical administration. 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.[51] [52]

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

As relevant to the present analysis, sodium thiosulfate was nominated for injectable (intravenous, intradermal, intramuscular, subcutaneous) administration for the treatment of calciphylaxis, cyanide toxicity, extravasation, and nephrotoxicity prophylaxis.

i. Calciphylaxis

The nominator proposes to produce an injectable compounded sodium thiosulfate drug product without potassium chloride to be 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 high for patients with renal disease or impairment. This assertion is inaccurate because the amount of potassium from the approved sodium thiosulfate product (440 mg of a 25 g dose) is small relative to the amount removed in a typical dialysis session (Refs. 14 and 15).[53]

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, it logically follows that a concentrated, compounded sodium thiosulfate product would also need to be diluted before administration for the same reason. 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).

Commenters on FDA's proposal not to include sodium thiosulfate on the 503B Bulks List continue to assert that there is a clinical need for potassium-free compounded sodium thiosulfate to treat calciphylaxis in hemodialysis patients. However, none of the literature pertaining to potassium referenced in the comments demonstrates that there is an attribute of the FDA-approved sodium thiosulfate drug product that makes it medically unsuitable to treat certain patients for calciphylaxis due to the presence of potassium in the approved product. None of the referenced literature pertaining to potassium provided additional justification or data to support the commenters' assertion that the amount of potassium in the approved sodium thiosulfate injectable product is clinically significant and problematic for some calciphylaxis patients receiving dialysis. We disagree that the potassium content in the approved sodium thiosulfate product poses an increased risk of hyperkalemia when used off-label for the management of calciphylaxis during hemodialysis. Patients on hemodialysis are generally permitted to take in potassium (*i.e.,* <3 g or ~70 milliequivalents (mEq/day). The amount of potassium being administered with the approved sodium thiosulfate product, *i.e.,* 440 mg of potassium chloride or ~ 6 mEq of potassium, is a fraction of the amount that the average dialysis patient is permitted per day.

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.[54]

ii. 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-

[50] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0173.

[51] 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.*

[52] Sodium thiosulfate is also approved for sequential use with sodium nitrite for intravenous administration.

[53] 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.,* Ref. 9 (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'') and Ref. 10 (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.'')

[54] 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 posed by the amount of potassium in the approved product to patients receiving sodium thiosulfate for the treatment of calciphylaxis.

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).[55] Sodium nitroprusside was also nominated separately (see FDA's analysis in the July 2020 notice), 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 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. No new information supporting the clinical need for compounding from the bulk drug substance sodium thiosulfate to make drug products for the treatment of cyanide toxicity was provided by the commenters.

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 and that the proposed compounded drug products are intended to address.

iii. Extravasation 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. No new information supporting the clinical need for compounding from the bulk drug substance sodium thiosulfate to make drug products for these uses was provided by the commenters. Accordingly, FDA finds no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address.

b. Whether the Drug Product Must Be Compounded From a Bulk Drug Substance

Because 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, 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 prepared using a bulk drug substance rather than an FDA-approved drug product.

c. Listing Determination for Sodium Thiosulfate (Except for Topical Administration)

In addition to the comments discussed above, two other commenters agreed with FDA's proposal not to include sodium thiosulfate on the 503B Bulks List. As discussed in more detail above, the information supporting the clinical need for compounding from the bulk drug substance sodium thiosulfate to produce drug products (except for topical administration) provided by the commenters does not alter FDA's view that there is no clinical need for compounding from the bulk drug substance for these uses. FDA therefore finds that there is no clinical need for compounding from the bulk drug substance sodium thiosulfate to produce drug products (except for topical administration) under section 503B of the FD&C Act, and we have determined that it will not be placed on the 503B Bulks List. Sodium thiosulfate for topical administration only remains under consideration by the Agency at this time, and as noted above may be eligible for the enforcement discretion policy described in FDA's Interim Policy provided the circumstances described in the guidance are present.

IV. Other Issues Raised in Nominations and Comments

Two commenters expressed concern that nominations submitted before FDA issued the Clinical Need Guidance in March 2019 are disadvantaged in demonstrating clinical need because the nominators might not have fully understood FDA's thinking on clinical need when they submitted their nominations.[56] In addition, one commenter expressed concern that FDA is evaluating bulk drug substances for clinical need pursuant to a non-binding guidance document. FDA disagrees with these comments. First, as explained in section II.B, FDA is evaluating bulk drug substances nominated for inclusion on the 503B Bulks List under the ''clinical need'' standard provided by the FD&C Act as amended by the Drug Quality and Security Act in 2013.[57] The analysis under the statutory ''clinical need'' standard described in this notice is consistent with the approach described in FDA's Clinical Need Guidance. Second, the commenters fail to note the many opportunities that nominators and interested members of the public had to provide information supporting a clinical need to compound drug products containing the bulk drug substances that are the subject of this notice. As explained in section II.A, a public docket, FDA–2015–N–3469, is available for interested persons to submit nominations, including updated or revised nominations, or comments on nominated substances. Furthermore, during the comment periods for the September 2019 and July 2020 **Federal Register** notices, commenters had an additional opportunity to submit comments to the docket associated with those notices to provide additional supporting information for the bulk drug substances that are the subject of this notice, and many did so. Moreover, in response to a request from a commenter, FDA reopened the comment period on the July 2020 **Federal Register** notice for an additional 30 days to allow interested persons yet another opportunity to submit additional comments.

Three commenters on the bulk drug substances addressed in this notice assert that FDA is regulating and interfering with the practice of medicine by not placing bulk drug substances on the 503B Bulks List despite some physicians wanting to prescribe drug products compounded from those bulk drug substances. FDA disagrees with these comments. The Agency's evaluation under the clinical need standard only regulates the ability of certain compounded drug products to reach the market and is well within the

[55] 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.

[56] See 84 FR 7383, which is available at *https://www.federalregister.gov/documents/2019/03/04/2019-03807/evaluation-of-bulk-drug-substances-nominated-for-use-in-compounding-under-section-503b-of-the.*

[57] See Public Law 113–54, § 102(a), (2013), which is available at *https://www.govinfo.gov/content/pkg/PLAW-113publ54/pdf/PLAW-113publ54.pdf.*

Agency's authorities.[58] The Agency is fulfilling its statutory mandate of regulating outsourcing facilities' production and distribution of compounded drug products, not interfering with physicians' clinical decisions regarding which drug products to prescribe. Indeed, a Federal court considered the very claim raised in these comments and determined that FDA's evaluation under the clinical need standard ''regulates the type of drug that reaches the marketplace,'' a decision that ''rests well within FDA's regulatory authority under the FDCA . . . and . . . does not intrude on the practice of medicine.'' [59]

One commenter expressed concern that FDA is promoting the off-label use of FDA-approved drug products. FDA disagrees with this comment. In performing the clinical need evaluation, FDA asks a limited, threshold question to determine whether there might be a clinical need for a compounded drug product, by asking what attributes of the approved drug product the proposed compounded drug product 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 drug products that include a needed change to an approved drug product rather than to compound drug products without such a change. We do not suggest that the approved drug product, or products prepared from it, are approved for the use proposed by the nomination being evaluated.

One commenter expressed concern with FDA's decision to evaluate clinical need in the context of the specific drug products proposed to be compounded in the nomination. These comments stated that requiring nominators to provide information on specific drug products is unnecessary to determine whether there is a clinical need for the bulk drug substance. This commenter also asserts that FDA should not evaluate bulk drug substances in the context of finished dosage forms for drug products. FDA disagrees with these comments. As explained in section I of this notice, section 503B of the FD&C Act limits the bulk drug substances that outsourcing facilities can use in compounding to those that are used to compound drugs in shortage or that appear on a list developed by FDA of bulk drug substances for which there is a clinical need.[60] Section 503B of the FD&C Act includes this limitation, among others, to help ensure that outsourcing facilities do not grow into conventional manufacturing operations making unapproved new drug products without complying with critical requirements, such as new drug approval. Outsourcing facilities, as opposed to other compounders, may compound and distribute drug products for ''office stock'' without first receiving a prescription for an individually identified patient [61] and without conditions on interstate distribution that are applicable to other compounded drugs.[62] Because of these differences and others, section 503B of the FD&C Act places different conditions on drugs compounded by outsourcing facilities, including limitation on the outsourcing facilities' use of bulk drug substances, which are more stringent than those placed on other compounders' use of bulk drug substances.[63] The clinical need standard in section 503B of the FD&C Act requires FDA to perform a sorting function—to distinguish bulk drug substances for which there is a clinical need from those for which there is not—and this requires the FDA to apply its expertise to consider whether there is a need for the finished drug product that would be compounded from the bulk drug substance. Indeed, a Federal court considered the very claim raised in these comments and determined that ''[o]nly when 'clinical need' is assessed against the availability and suitability of an approved drug does the term perform the classifying function that Congress intended.'' In reaching this view, the court found that only when the clinical need evaluation ''considers the actual way in which the active pharmaceutical ingredient supplies a therapeutic benefit—by its administration as a finished drug product—does the inquiry produce the categorization that Congress surely envisioned'' in enacting section 503B of the FD&C Act.[64] FDA's clinical need assessments help limit patient exposure to compounded drug products that have not been demonstrated to be safe and effective to those situations in which the compounded drug product is necessary for patient treatment. In addition, FDA's assessments preserve the incentives for applicants to invest in the research and testing required to obtain FDA approval and continue to manufacture FDA-approved drug products, thereby helping to maintain a supply of high-quality, safe, and effective drugs.

Some of the bulk drug substance nominations and comments assert that there could be a benefit gained from using a bulk drug substance to compound drug products that do not require the manipulations that the approved drug products that contain these bulk drug substances require before they can be administered (*e.g.,* dilution or drawing the drug into a syringe before administration). As explained above, when a bulk drug substance is a component of an approved drug, we asked whether there

[58] See *United States* v. *Evers,* 643 F.2d 1043, 1048 (5th Cir. 1981) (''[W]hile the [FDCA] was not intended to regulate the practice of medicine, it was obviously intended to control the availability of drugs for prescribing by physicians.''); *United States* v. *Regenerative Scis., LLC,* 741 F.3d 1314, 1319–20 (DC Cir. 2014); (citing Evers and noting that the FDCA ''regulate[s] the distribution of drugs by licensed physicians''); *Gonzales* v. *Raich,* 545 U.S. 1, 28 (2005) (''the dispensing of new drugs, even when doctors approve their use must await federal approval.'').

[59] *Athenex Inc.* v. *Azar,* 397 F. Supp. 3d 56, 72 (D.D.C. 2019).

[60] Section 503B(a)(2(A)(i) and (ii) of the FD&C Act.

[61] By contrast, to qualify for the exemptions in section 503A of the FD&C Act, drug products compounded by licensed pharmacists in State-licensed pharmacies or Federal facilities, or by licensed physicians, must be compounded be based on the receipt of a valid prescription for an individually identified patient. This means that for drug products compounded under section 503A to meet the conditions of that section and qualify for the exemptions in the statute, the pharmacist or physician compounding under section 503A of the FD&C Act must compound either: (1) After receiving a valid prescription for an identified, individual patient or (2) before receiving a patient-specific prescription, in limited quantities, based on a history of receiving valid orders generated solely within the context of an established relationship with the patient or prescriber. See FDA's final guidance for industry ''Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act'' (December 2016) (Ref. 13).

[62] For drug products compounded under section 503A of the FD&C Act to meet the conditions of that section and qualify for the exemptions in the statute, drug products must be compounded in a State; (i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State or (ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician (see section 503A(b)(3)(a)(B)(i) and (ii) of the FD&C Act).

[63] Licensed pharmacies and physicians who compound drugs under the conditions of section 503A of the FD&C Act, including the requirement to compound drugs only pursuant to a prescription for an identified individual patient, may use many bulk drug substances by operation of the statute, without action by FDA. See section 503A(b)(1)(A)(i)(I) and (II) of the FD&C Act (providing that a drug product may be compounded consistent with the exemptions in section 503A of the FD&C Act if the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapters on pharmacy compounding; or if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary).

[64] *Athenex Inc.* at 65.

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 and comments 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.

Two comments requested changes to the Interim Policy. These comments are outside the scope of FDA's bulk drug substance evaluations and decisions that are the subject of this notice. FDA welcomes public comments on its guidance documents that address human drug compounding. We encourage comments on the Interim Policy to be submitted the docket for the guidance, docket number FDA–2015–D–3539. Comments may be submitted to this docket at any time on *https://www.regulations.gov.*

V. Conclusion

For the reasons stated above, we find that there is a clinical need for outsourcing facilities to compound using the bulk drug substances DPCP for topical use only, glycolic acid for topical use only in concentrations up to 70 percent, SADBE for topical use only, and TCA for topical use only and, therefore, we are now including them on the 503B Bulks List. In addition, we find that there is no clinical need for outsourcing facilities to compound using the bulk drug substances diazepam, dipyridamole, dobutamine HCl, dopamine HCl, edetate calcium disodium, folic acid, glycopyrrolate, and sodium thiosulfate (except for topical administration), and therefore we are not including 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.

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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 *https://ijdvl.com/comparative-study-of-trichloroacetic-acid-versus-glycolic-acid-chemical-peels-in-the-treatment-of-melasma/.*

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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.

*13. FDA Guidance for Industry, Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act, December 2016 (available at *https://www.fda.gov/media/97347/download*).

14. Pun, Patrick H. and John P. Middleton, 2017, ''Dialysate Potassium, Dialysate Magnesium, and Hemodialysis Risk,'' *Journal of the American Society of Nephrology,* 28: 3441–3451.

15. De Nicola, L., V. Bellizzi, R. Minutolo, et al., 2000, ''Effect of Dialysate Sodium Concentration on Interdialytic Increase of Potassium,'' *Journal of the American Society of Nephrology,* 11:2337–2343.

Dated: January 21, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2022–D–0092]

Revising Abbreviated New Drug Application Labeling Following Revision of the Reference Listed Drug Labeling; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled ''Revising ANDA Labeling Following Revision of the RLD Labeling.'' This guidance provides recommendations for updating labeling for abbreviated new drug applications (ANDAs) following revisions to the labeling of a reference listed drug (RLD), including information on how to identify RLD labeling updates and how to submit labeling updates to both unapproved and approved ANDAs to conform to RLD labeling updates. This draft guidance revises the guidance for industry entitled ''Revising ANDA Labeling Following Revision of the RLD Labeling'' issued in April 2000.