Proposed Project

National Surveillance of Community Water Systems and Corresponding Populations with the Recommended Fluoridation Level (OMB Control No. 0920–1319, Exp. 2/29/2024)—Extension—National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), Centers for Disease Control and Prevention (CDC).

Background and Brief Description

Community water fluoridation is the process of adjusting the fluoride concentration of a community water system (CWS) to the level beneficial for prevention of dental caries as recommended by the U.S. Public Health Service (PHS). Community water fluoridation is a major factor contributing to the large decline in caries in the U.S. in the past 75 years and is recognized as one of 10 great public health achievements of the twentieth century. Community water fluoridation reduces dental caries by 25% and is a safe and the cost-effective way to deliver fluoride to people of all ages, regardless of education and income level. It is especially important for populations with limited access to preventive dental measures.

CDC is authorized to collect the information under the U.S. Public Health Service Act. This data collection aligns with CDC's strategy to use public health surveillance to inform programs and policies to improve the oral health of the nation by reducing disparities and expanding access to effective prevention programs. CDC uses the Water Fluoridation Reporting System (WFRS) to collect water fluoridation coverage and quality throughout the U.S. This data allows CDC and States to monitor the performance and efficiency of their water fluoridation programs, which will improve and extend program delivery. Respondents to the information collection are State fluoridation managers or other State government officials designated by the State dental director or drinking water administrator. State participation in the data collection is voluntary.

CDC requests OMB approval for an estimated 2,824 annual burden hours. There is no cost to respondents other than their time to participate.

ESTIMATED ANNUALIZED BURDEN HOURS

Type of respondents	Form name	Number of respondents	Number of responses per respondent	Average burden per response (in hours)	Total burden (in hours)
State Official	Fluoridation status and population	50	1	38	1,900
State Official	Fluoride testing data	33	1	28	924
Total					2,824

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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 (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 two bulk drug substances that FDA has considered and is not including on the list at this time: ephedrine sulfate and hydroxychloroquine sulfate. 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 August 21, 2023.

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

FOR FURTHER INFORMATION CONTACT: Tracy Rupp, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Silver Spring, MD 20993, 301–796–3100.

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 set forth 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

[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 an exemption from CGMP requirements).

[3] Section 503B(b)(4) and (5) of the FD&C Act.

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]

FDA has published a series of **Federal Register** notices addressing bulk drug substances nominated for inclusion on the 503B Bulks List.[7] This notice identifies two bulk drug substances that FDA has considered and is not including on the 503B Bulks List.

For purposes of section 503B of the FD&C Act, *bulk drug substance* means an active pharmaceutical ingredient as defined in 21 CFR 207.1.[8] *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.[9] [10]

II. Methodology for Developing the 503B Bulks List

A. Process for Developing the List

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

[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] 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), March 24, 2021 (86 FR 15673), November 23, 2022 (87 FR 71642), and April 6, 2023 (88 FR 20531). 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. FDA has not yet reached a final determination on whether each of the substances evaluated in the September 2019, July 2020, or March 2021 notices will be added to the 503B Bulks List. In addition, bumetanide, which was considered in the August 2018 notice, remains under consideration by the Agency.

[8] See section 503B(a)(2) of the FD&C Act, which defines bulk drug substances used in compounding under section 503B according to 21 CFR 207.3(a)(4) ''or any successor regulation.'' 21 CFR 207.1 is the successor regulation.

[9] Section 503B(a)(2) of the FD&C Act and 21 CFR 207.1.

[10] Inactive ingredients are not subject to section 503B(a)(2) of the FD&C Act and will not be included in the 503B Bulks List because they are not included within the definition of a bulk drug substance. Pursuant to section 503B(a)(3), inactive ingredients used in compounding must comply with the standards of an applicable U.S. Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists.

[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.

[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 FDA's evaluation 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.* We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at *https://www.fda.gov/regulatory-information/search-fda-guidance-documents.*

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.[14] In applying this standard to make its determinations regarding the substances set forth in this notice, FDA interprets 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 does not interpret 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 a bulk drug substance 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, FDA does not consider convenience in administering a particular compounded drug product (*e.g.,* a ready-to-use form) or the cost of the compounded drug product as compared with an FDA-approved drug product when assessing ''clinical need.''

Both bulk drug substances addressed in this notice, ephedrine sulfate and hydroxychloroquine sulfate, are components of FDA-approved drug products. FDA therefore began its evaluation by asking one or both, as applicable, 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 FDA-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 FDA-approved drug product, there are certain benefits of doing so over starting with a bulk drug substance, including that FDA-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 an FDA-approved drug or compounding starting with an FDA-approved drug product. FDA did not answer ''yes'' to both of the threshold questions for the two bulk drug substances that are components of FDA-approved drug products that we are addressing in this notice. Accordingly, as explained below, we did not proceed further in our evaluation of these substances and have decided not to include them on the 503B Bulks List.

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

The two 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 ephedrine sulfate (Refs. 1 and 2) and hydroxychloroquine sulfate (Ref. 3).

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).[15] In the present notice, after review of the comments submitted to the docket for the September 2019 notice, FDA is making its final determination not to include ephedrine sulfate on the 503B Bulks List. At this time, FDA is not making a final determination regarding famotidine, hydralazine HCl, sodium tetradecyl sulfate, trypan blue, and vecuronium bromide.[16] These substances remain under consideration by FDA.

In March 2021, the Agency issued a **Federal Register** notice in which it evaluated five nominated bulk drug substances under the section 503B statutory standard (the March 2021 notice).[17] FDA proposed to include quinacrine hydrochloride (for oral use only) on the 503B Bulks List. FDA proposed not to include bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate on the 503B Bulks List. In April 2023, after review of comments submitted to the March 2021 docket, the Agency issued a **Federal Register** notice, making its final determination to include quinacrine hydrochloride on the 503B Bulks List to compound drug products for oral use only.[18] In the present notice, after review of the comments submitted to the docket for the March 2021 notice, FDA is making its final determination

[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] See 84 FR 46014.

[16] FDA made a final determination not to include dipyridamole on the 503B Bulks List (see 87 FR 4240). FDA made a final determination not to include methacholine chloride and sodium bicarbonate on the 503B Bulks List (see 88 FR 20531).

[17] 86 FR 15673.

[18] 88 FR 20531.

not to include hydroxychloroquine sulfate on the 503B Bulks List. At this time, FDA is not making a final determination regarding bromfenac sodium, mitomycin-C, and nepafenac. These substances remain under consideration by FDA.

Because both ephedrine sulfate and hydroxychloroquine sulfate 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(s) proposed to be compounded is intended to address that attribute in each FDA-approved drug product and (2) is there a basis to conclude that the drug product(s) proposed to be compounded must be compounded using a bulk drug substance. FDA considered comments to the docket submitted within the public comment period, but as explained below, none of the comments received on these bulk drug substances provided information that led FDA to change its determination.

A. Ephedrine Sulfate

Ephedrine sulfate was nominated for inclusion on the 503B Bulks List to compound drug products to treat acute bronchospasm, drug induced hypotension due to anesthesia, and nasal congestion.[19] The proposed route of administration is intravenous, the proposed dosage form is a preservative-free solution, and the proposed strengths are 5 mg/mL and 10 mg/mL.[20] During the comment period for the September 2019 notice, a commenter proposed that there was a clinical need to compound higher concentration ephedrine sulfate drug products to treat priapism. The proposed route of administration for this new proposed use is intracorporeal, the proposed dosage form is a solution, and the proposed strength is 100 mg/mL.[21] Because additional references were provided supporting this proposed use and route of administration, FDA considered this use and this route of administration before reaching a final clinical need determination (Ref. 2).

As noted above, ephedrine sulfate is a component of FDA-approved drug products (*e.g.,* NDAs 208943 and 208289). FDA-approved ephedrine sulfate is available as a 1 mL single-dose drug product that contains 50 mg/mL (50 mg/mL) ephedrine sulfate, preservative-free, for intravenous administration, and as a 10 mL multi-dose vial that contains 500 mg/10 mL (50 mg/mL) ephedrine sulfate, with preservative, for intravenous administration.[22] These ephedrine sulfate drug products must be diluted before administration to achieve the desired concentration for their labeled indications. Ephedrine sulfate is also available as a 5 mL single dose, prefilled syringe that contains 25 mg/5 mL (5 mg/mL) ephedrine sulfate, preservative-free, for intravenous administration, and as a 10 mL single dose, prefilled syringe that contains 50 mg/10 mL (5 mg/mL) ephedrine sulfate, preservative-free, for intravenous administration.[23] The products available as prefilled syringes are premixed formulations and do not require dilution prior to administration for their labeled indications.

1. Suitability of FDA-Approved Drug Product

In its proposal to not include ephedrine sulfate on the 503B Bulks List, FDA explained that the nominations did not identify an attribute of the FDA-approved drug products that make them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. Several comments received agreed with FDA's proposal not to include ephedrine sulfate on the 503B Bulks List.[24] Several comments were not supportive. However, none of the comments received on FDA's proposal provided information that led FDA to change its position on this question. A commenter stated that there is a clinical need for an intracorporeal, single-ingredient, higher concentration ephedrine sulfate compounded drug product for use to treat priapism.[25] However, the commenter failed to identify an attribute of the FDA-approved drug products, including the intravenous formulations of ephedrine sulfate 50 mg/mL solution for dilution (*e.g.,* NDA 208943), that is medically unsuitable for patients with priapism or identify an attribute of the FDA-approved products that the proposed compounded drug product is intended to address. The FDA-approved products are available in the concentration of 50 mg/mL (undiluted) and can be administered in a sufficient volume or in multiple doses to achieve the proposed dose of 100 mg for the treatment of priapism.[26] [27] A commenter also stated that the FDA-approved ephedrine sulfate products are not compatible with new technology such as syringe-robotics and vial docking technology to easily make stock

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

[20] Nominator(s) proposed to compound a preservative-free solution. However, they failed to acknowledge that there is a preservative-free formulation of ephedrine sulfate that is marketed or explain why that formulation would be medically unsuitable for certain patients. Additionally, since the September 2019 notice, ephedrine sulfate has been FDA-approved as a preservative-free, 25 mg/5mL (5 mg/mL) single dose, premixed, labeled syringe (not for dilution) (See NDA 213407 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/3155f177-4aff-4560-9f7c-f77649d065d9/3155f177-4aff-4560-9f7c-f77649d065d9.xml*) and a preservative-free, 50 mg/10mL (5 mg/mL) single dose, premixed vial (See NDA 213407 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/54276f21-7800-44f4-ae51-0060fb1c43ad/54276f21-7800-44f4-ae51-0060fb1c43ad.xml*).

[21] See Docket No. FDA–2018–N–3240, document no. FDA–2018–N–3240–0047. Other commenters proposed additional uses and routes of administration: intramuscular administration of a higher concentration of ephedrine sulfate for postoperative nausea and vomiting refractory to traditional antiemetics; intravenous or intrathecal administration of ephedrine sulfate for hypotension in patients that received a certain type of anesthesia or received an overdose of a drug that can lower blood pressure; and continuous (intravenous) infusion to prevent hypotension secondary to spinal anesthesia during cesarean section. These other uses will not be considered further because the commenters either proposed uses or routes of administration already evaluated in the September 2019 notice and the literature provided in the comments did not contain any new information that would support FDA's reconsideration of its proposal on the substance, or the commenters proposed new uses or routes of administration but did not provide sufficient information, including citations to relevant literature, supporting a clinical need.

[22] See, *e.g.,* NDAs 208943 and 208289.

[23] See, *e.g.,* NDAs 208289 and NDA 213407.

[24] See Docket No. FDA–2018–N–3240, document nos. FDA–2018–N–3240–0043, FDA–2018–N–3240–0045, FDA–2018–N–3240–0050, FDA–2018–N–3240–0052.

[25] See Docket No. FDA–2018–N–3240, document no. FDA–2018–N–3240–0047.

[26] In noting this issue, we do not mean to suggest or imply that the approved drug products, or products prepared from them, are approved for the use proposed by the commenter. For the Part 1.a. analysis we asked a limited, threshold question to determine whether there might be clinical need for a compounded drug product, by asking what attributes of the FDA-approved drug the proposed compounded drug would change, and why. Because this proposed product did not pass through Part 1.a. (for the reasons described in the memo) we did not reach Part 2 and therefore did not consider the Part 2 factors, including the available evidence of effectiveness or lack of effectiveness of a drug product compounded with ephedrine sulfate. FDA-approved ephedrine sulfate 50 mg/mL solution for dilution has not been shown to be safe and effective for intracorporal administration to treat priapism.

[27] The commenter proposes that in order to achieve a 100 mg/mL dose, more than one vial of FDA-approved ephedrine sulfate is needed. While there is a 50 mg/mL formulation that is available in 1 mL vials, there is also an FDA-approved formulation of intravenous ephedrine sulfate solution that is available as a 500 mg/10 mL vial (dilution required). In order to achieve the 100 mg/mL dose, 2 mL of ephedrine sulfate could be used.

solutions to produce onsite.[28] However, FDA is not aware of issues with using the FDA-approved product when the compounding process and equipment are appropriately selected. Additionally, these arguments do not take into account the approval by FDA of two ephedrine sulfate drug products that are pre-diluted and thus would not need additional manipulation at the bedside by a medical provider before use for their labeled indications.[29] Commenters also made various arguments addressing supply issues, convenience, and cost.[30] However, as explained above, FDA does not consider supply issues, convenience, and costs to be within the meaning of ''clinical need'' for compounding with a bulk drug substance under section 503B of the FD&C Act. Accordingly, with respect to the ephedrine sulfate drug products proposed to be compounded, FDA finds no basis to conclude that an attribute of the FDA-approved product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation.

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

The nominations do not provide support for the position that drug products containing ephedrine sulfate must be compounded from bulk drug substances rather than the approved drug product. No further information was supplied during the comment period that supports the need for compounding ephedrine sulfate drug products from bulk drug substances. Because there is no basis to conclude that an attribute of the FDA-approved ephedrine sulfate products makes them medically unsuitable for some patients; however, FDA has not considered whether there is a basis to conclude that the proposed compounded products must be made from a bulk drug substance rather than from an FDA-approved product.

B. Hydroxychloroquine Sulfate

Hydroxychloroquine sulfate was nominated for inclusion on the 503B Bulks List to compound drug products to treat rheumatoid arthritis and juvenile arthritis (also known as juvenile idiopathic arthritis).[31] The proposed route of administration is oral, the proposed dosage forms are a capsule or suspension, and the proposed doses or concentrations are 200 to 500 mg capsules and 100 to 200 mg/mL suspension. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* NDA 009768, ANDA 040104, and ANDA 213342).[32] [33] [34]

FDA-approved hydroxychloroquine sulfate is available as 200 mg (equivalent to 155 mg of hydroxychloroquine base), film-coated tablets for oral administration.[35]

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

As described in FDA's preliminary **Federal Register** notice addressing this substance, there is a basis to conclude that an attribute of the approved hydroxychloroquine sulfate tablets for oral administration makes them medically unsuitable for the treatment of some patients with rheumatoid arthritis and juvenile arthritis.[36] The nomination suggested that the FDA-approved oral tablets, a solid oral dosage form, are medically unsuitable in pediatric patients who are unable to swallow tablets. We agree that there may be certain patients for whom the approved oral tablets are medically unsuitable, and this would depend on a patient's clinical presentation and age, among other considerations. As a general matter, the drug product proposed to be compounded appears to address the potential unsuitability of a solid oral dosage form because the nominator proposes to compound a suspension of hydroxychloroquine sulfate for oral administration.

The nomination further states that ''pediatric dosing is not standardized but weight-based, making getting the correct dose difficult with tablets.'' We agree that an oral suspension could allow for more flexible dosing when compared to the approved tablets when following weight-based dosing recommendations, and that this also supports the proposition that the approved product may be unsuitable for certain patients.[37]

In addition to the proposed suspension, the nomination also proposes that there is a clinical need to compound hydroxychloroquine sulfate 200 to 500 mg capsules for oral administration. The nomination does not explain how the proposed compounded capsule products are intended to address the medical unsuitability of the approved product. Similar to tablets, capsules are less flexible in dosing and would be difficult for patients to take if they are unable to swallow tablets. In addition, the nomination does not identify any data or information as to the need for compounded products with a higher concentration than the approved product. No further information was supplied on this point during the comment period.

The nomination also claims that some patients are ''unable to tolerate excipients'' in the approved product, but the nomination does not identify which excipients they are referring to, nor do they provide any data or information supporting how the proposed drug products will address that particular attribute. No further information was supplied on this point during the comment period.

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

Because there is a basis to conclude that an attribute of the approved hydroxychloroquine sulfate tablets makes them medically unsuitable for some patients, and the proposed compounded oral suspension is intended to address that attribute, FDA

[28] See Docket No. FDA–2018–N–3240, document no. FDA–2018–N–3240–0047.

[29] See footnote 20 above.

[30] See Docket No. FDA–2018–N–3240, document nos. FDA–2018–N–3240–0053, FDA–2018–N–3240–0049, and FDA–2018–N–3240–0047.

[31] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0165.

[32] See, *e.g.,* NDA 009768 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.*

[33] See, *e.g.,* ANDA 040104 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/e5375cf7-9423-40a4-bd33-ce5812da4a73/e5375cf7-9423-40a4-bd33-ce5812da4a73.xml.*

[34] See, *e.g.,* ANDA 213342 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/a594d892-e496-38f5-e053-2a95a90a9da8/a594d892-e496-38f5-e053-2a95a90a9da8.xml.*

[35] See, *e.g.,* NDA 009768 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/009768s037s045s047lbl.pdf.*

[36] In noting this issue, we do not mean to suggest or imply that the approved drug products, or products prepared from them, are approved for all of the uses proposed by the nomination. For the question 1 analysis we asked 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 the proposed compounded drug would change, and why. Because this nomination did not pass through question 2, we did not reach the balancing test and therefore did not consider the four factors, including the available evidence of effectiveness or lack of effectiveness of a drug product compounded with hydroxychloroquine sulfate. The safety and efficacy of chronic use of hydroxychloroquine sulfate have not been established for juvenile idiopathic arthritis.

[37] We note that the nominator's proposed concentration of 100 to 200 mg/mL would offer little benefit in the younger aged pediatric population because a suspension at this strength would likely require administration of small volumes (*e.g.,* ≤1 mL). We are aware of several published pharmacy compounding formulations for hydroxychloroquine sulfate 25 mg/mL suspensions (Refs. 4 to 6), which may be more suitable for the younger pediatric population.

next considers whether there is a basis to conclude that the proposed oral suspension must be made from a bulk drug substance rather than from an FDA-approved product. The approved hydroxychloroquine sulfate drug products are 200 mg immediate release tablets with film coating.[38]

As described in FDA's preliminary **Federal Register** notice addressing this substance, although the approved products are film-coated, the coating is not intended to change/control the release profile. FDA is not aware of issues with using the FDA-approved product when the compounding process and equipment are appropriately selected. No further information was supplied on this point during the comment period. We also note that there is a draft USP monograph for the compounded suspension that uses an FDA-approved film-coated tablet as the starting material (Ref. 6).[39] As with all suspensions, the particle size of the powder should be carefully controlled and the density of suspension vehicle should be selected appropriately in order to make the oral suspension uniform and stable, which can affect the dose administrated to the patients.

One commenter supported FDA's proposal not to include hydroxychloroquine sulfate on the 503B Bulks List. Commenters provided no new information supporting the clinical need for compounding from the bulk drug substance hydroxychloroquine sulfate. Because we do not find a basis to conclude that a bulk drug substance is needed to compound the proposed compounded hydroxychloroquine sulfate oral suspension, rather than starting with the FDA-approved product, we do not find a clinical need to include hydroxychloroquine sulfate on the 503B Bulks List under question 2.

IV. Other Issues Raised in Nominations and Comments

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.[40] In addition, there was also concern expressed about whether 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 of this notice, 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.[41] 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, there have been many opportunities for nominators and interested members of the public 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 March 2021 **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.

Another issue raised was whether 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 Agency's authorities.[42] 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 [FD&C Act] . . . and . . . does not intrude on the practice of medicine.'' [43]

Another concern was the possibility that FDA is promoting the off-label use of FDA-approved drug products. FDA disagrees that it is promoting the off-label use of FDA-approved drug products. 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.

Regarding FDA's decision to evaluate clinical need in the context of the specific drug products proposed to be compounded in the nomination, a concern was raised 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 and 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.[44] Section 503B of the FD&C Act includes this limitation, among others,

[38] The tablet is not scored. The approved product labeling states that the ''film-coated tablets cannot be divided, therefore they should not be used to treat patients who weigh less than 31 kg.''

[39] We note that the product labeling for hydroxychloroquine sulfate film-coated tablets (*e.g.,* NDA 009768, ANDA 213342) states, ''Do not crush or divide hydroxychloroquine sulfate film-coated tablets.'' However, this does not change our view that the product can be compounded starting with the approved drug product.

[40] See 84 FR 7390, 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.*

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

[42] See *United States* v. *Evers,* 643 F.2d 1043, 1048 (5th Cir. 1981) (''[W]hile the [FD&C Act] 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 (D.C. Cir. 2014); (citing *Evers* and noting that the FD&C Act ''regulate[s] the distribution of drugs by licensed physicians''); *Gonzales* v. *Raich,* 545 U.S. 1, 28 (2005) (''[T]he dispensing of new drugs, even when doctors approve their use must await federal approval.'').

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

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

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 [45] and without conditions on interstate distribution that are applicable to other compounded drugs.[46] 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.[47] 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 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.'' [48] 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.[49] 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.

Finally, changes to the Interim Policy were requested. 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. Comments on the Interim Policy may be submitted to the docket for the guidance, Docket No. FDA–2015–D–3539, at any time at *https://www.regulations.gov.*

V. Conclusion

For the reasons stated above, we find that there is no clinical need for outsourcing facilities to compound using the bulk drug substances ephedrine sulfate and hydroxychloroquine sulfate, and therefore we are not including these bulk drug substances on the 503B Bulks List.

VI. 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 Memorandum to File, ''Clinical Need for Ephedrine Sulfate in Compounding Under Section 503B of the FD&C Act,'' March 2021.

*2. FDA Memorandum to File, ''Clinical Need Supplemental Memorandum for Ephedrine Sulfate in Compounding Under Section 503B of the FD&C Act,'' August 2023.

*3. FDA Memorandum to File, ''Clinical Need for Hydroxychloroquine Sulfate in Compounding Under Section 503B of the FD&C Act,'' March 2021.

4. McHenry, A.R., M.F. Wempe, and P.J. Rice, (2017) ''Stability of Extemporaneously Prepared Hydroxychloroquine Sulfate 25-mg/mL Suspensions in Plastic Bottles and Syringes,'' *International Journal of Pharmaceutical Compounding,* 21(3), 251–254 (APA). Retrieved from *https://ijpc.com/Abstracts/Abstract.cfm?ABS=4322.*

5. American Society of Hospital Pharmacists (ASHP 2020), ''Hydroxychloroquine Sulfate Suspension 25 mg/mL.'' Retrieved from *www.ashp.org.*

6. USP 2020, ''USP Draft Compounded Preparation Monograph for Hydroxychloroquine Sulfate Compounded Oral Suspension.'' Published for public comment in *Pharmacopeial Forum* 46(2). Retrieved from *https://go.usp.org/l/323321/2020-04-08/33wcg6.*

Dated: August 15, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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[45] 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 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).

[46] 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). *See also* 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*).

[47] 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 chapter on pharmacy compounding; or if such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary).

[48] *Athenex Inc.,* 397 F. Supp. 3d at 65.

[49] *Id.*