Northern Mariana Islands, Guam, Puerto Rico, and Virgin Islands).

ANNUAL BURDEN ESTIMATES

Instrument	Annual number of respondents	Annual number of responses per respondent	Average burden hours per response	Annual burden hours
Child Care and Development Fund ACF–696 Financial Report	56	4	5	1120

Estimated Total Annual Burden Hours: 1120.

Authority: Section 658G(d), Pub. L. 113–186, 128 Stat. 1971.

Mary B. Jones,

ACF/OPRE Certifying Officer.

[FR Doc. 2021–05991 Filed 3–23–21; 8:45 am]

BILLING CODE 4184–43–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Submission for OMB Review; Child Care and Development Fund (CCDF) ACF–696T Financial Report (OMB #0970–0195)

AGENCY: Office of Child Care, Administration for Children and Families, HHS.

ACTION: Request for public comment.

SUMMARY: The Administration for Children and Families (ACF) is requesting a 3-year extension of the form ACF–696T: Child Care and Development Fund Annual Financial Report. This form is currently approved under the ACF Generic Clearance for Financial Reports (OMB #0970–0510; expiration May 31, 2021), and ACF is proposing to reinstate the previous OMB number under which this form had been approved. There are no changes requested to the form.

DATES: *Comments due within 30 days of publication.* OMB must make a decision about the collection of information between 30 and 60 days after publication of this document in the **Federal Register**. Therefore, a comment is best assured of having its full effect if OMB receives it within 30 days of publication.

ADDRESSES: Written comments and recommendations for the proposed information collection should be sent within 30 days of publication of this notice to *www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under 30-day Review—Open for Public Comments'' or by using the search function.

SUPPLEMENTARY INFORMATION:

Description: The ACF–696T Financial Report along with the instruction for completion of Form ACF–696T Financial Reporting Form for the Child Care and Development Fund (CCDF) are being submitted for renewal with no changes under a previous OMB number. The form collects CCDF financial expenditures data for the 221 Tribal Lead Agencies that receive CCDF funding. This report form is submitted annually by the referenced CCDF grant recipients. The form collects expenditures data for all respondents that receive CCDF funding.

Respondents: The 221 Tribal Lead Agencies that receive CCDF funding.

ANNUAL BURDEN ESTIMATES

Instrument	Annual number of respondents	Annual number of responses per respondent	Annual burden hours per response	Annual burden hours
Child Care and Development Fund ACF–696T Financial Report	221	1	5	1105

Estimated Total Annual Burden Hours: 1105.

Authority: Section 658G(d), Pub. L. 113–186, 128 Stat. 1971.

Mary B. Jones,

ACF/OPRE Certifying Officer.

[FR Doc. 2021–05992 Filed 3–23–21; 8:45 am]

BILLING CODE 4184–43–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2018–N–3240]

List of Bulk Drug Substances for Which There Is a Clinical Need Under the Federal Food, Drug, and Cosmetic Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is developing a list of bulk drug substances (active pharmaceutical ingredients) for which there is a clinical need (the 503B Bulks List). Drug products that outsourcing facilities compound using bulk drug substances on the 503B Bulks List can qualify for certain exemptions from the Federal Food, Drug, and Cosmetic Act (FD&C Act) provided certain conditions are met. This notice identifies one bulk drug substance that FDA has considered and proposes to include on the 503B Bulks List: Quinacrine hydrochloride (''quinacrine''). This notice identifies four bulk drug substances that FDA has considered and proposes not to include on the list: Bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate. Additional bulk drug substances nominated by the public for inclusion on this list are currently under consideration and may be the subject of future notices.

DATES: Submit either electronic or written comments on the notice by May 24, 2021.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before May 24, 2021. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of May 24, 2021. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

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

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

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

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

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

SUPPLEMENTARY INFORMATION:

I. Background

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions that must be satisfied for drug products compounded by an outsourcing facility to be exempt from section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)), section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use), and section 582 of the FD&C Act (21 U.S.C. 360eee–1) (concerning drug supply chain security requirements).[1]

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

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

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

[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.

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 one bulk drug substance that FDA has considered and proposes to include on the 503B Bulks List and four bulk drug substances that FDA has considered and proposes not to include on the 503B Bulks List.

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

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

II. Methodology for Developing the 503B Bulks List

A. Process for Developing the List

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

As FDA evaluates bulk drug substances, it intends to publish notices for public comment in the **Federal Register** that describe the FDA's proposed position on each substance along with the rationale for that position.[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 list identifying the bulk drug substances for which it has determined there is a clinical need and FDA's rationale in making that final determination. FDA will also publish in the **Federal Register** a list of those substances it considered but found that there is no clinical need to use in compounding and FDA's rationale in making this decision.

FDA intends to maintain a 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 where it has determined there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance. If a clinical need to compound drug products using the bulk drug substance has not been demonstrated, based on the information submitted by the nominator and any other information considered by the Agency, FDA will not place a bulk drug substance on the 503B Bulks List.

FDA 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 currently evaluating bulk drug substances that were nominated for inclusion on the 503B Bulks List, proceeding case by case, under the clinical need standard provided by the statute (Ref. 2).[14] In applying this standard to develop the proposals in this notice, FDA is interpreting the phrase ''bulk drug substances for which there is a clinical need'' to mean that the 503B Bulks List may include a bulk drug substance if: (1) There is a clinical need for an outsourcing facility to compound the drug product and (2) the drug product must be compounded using the bulk drug substance. FDA is not interpreting supply issues, such as backorders, to be within the meaning of ''clinical need'' for compounding with a bulk drug substance. Section 503B separately provides for compounding from bulk drug substances under the exemptions from the FD&C Act

[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), and July 31, 2020 (85 FR 46126). 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 the substances evaluated in the September 2019 or July 2020 notice 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] 21 CFR 207.3.

[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) of the FD&C Act, inactive ingredients used in compounding must comply with the standards of an applicable U.S. Pharmacopeia (USP) or National Formulary monograph, if a monograph exists.

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

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

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

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

discussed above if the drug product compounded from the bulk drug substance is on the FDA drug shortage list at the time of compounding, distribution, and dispensing. Additionally, we are not considering cost of the compounded drug product as compared with an FDA-approved drug product to be within the meaning of ''clinical need.''

Some of the bulk drug substances that we are addressing in this notice are components of FDA-approved drug products,[15] and we therefore began our evaluation of these bulk drug substances 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 compounded using a bulk drug substance that is a component of the approved drug is intended to address that attribute, there is no clinical need to compound a drug product using that bulk drug substance. Rather, such compounding would unnecessarily expose patients to the risks associated with drug products that do not meet the standards applicable to FDA-approved drug products for safety, effectiveness, quality, and labeling and would undermine the drug approval process. The reason for question 2 is that to place a bulk drug substance on the 503B Bulks List, FDA must determine that there is a clinical need for outsourcing facilities to compound a drug product *using the bulk drug substance* rather than starting with an FDA-approved drug product.

If the answer to both of these questions is ''yes,'' there may be a clinical need for outsourcing facilities to compound using the bulk drug substance, and we would evaluate the substance further, applying the factors described below. If the answer to either of these questions is ''no,'' we generally would not include the bulk drug substance on the 503B Bulks List, because there would not be a basis to conclude that there may be a clinical need to compound drug products using the bulk drug substance instead of administering or compounding starting with an approved drug product. FDA did not answer ''yes'' to both of the threshold questions for the four bulk drug substances that are components of approved drug products that we are addressing in this notice. Accordingly, as explained further below, we did not proceed further in our evaluation of these substances and are proposing not to include them on the 503B Bulks List.

With respect to one bulk drug substance we are addressing in this notice that is not a component of an FDA-approved drug product, quinacrine, we are conducting a balancing test with four factors, considering each factor in the context of the others and balancing them to determine whether the statutory ''clinical need'' standard has been 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 references in peer-reviewed medical literature.

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

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

In preparing its proposal to include a substance on 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 proposed entry on the 503B Bulks List to reflect its findings related to clinical need for the bulk substance proposed for inclusion on the list. Specifically, the proposed entry would authorize use of this bulk drug substance to compound drug products for oral use only.[16]

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

Because the substance in this section is not a component of an FDA-approved drug product, we applied the balancing test described above. The bulk drug substance that has been evaluated and that FDA is proposing to place on the 503B Bulks List is quinacrine HCl. The reasons for FDA's proposal is included below (Ref. 3).[17]

Quinacrine

FDA nominated quinacrine as a bulk drug substance for the 503B Bulks List to compound drug products in oral dosage forms at strengths of 25–100 milligram (mg) for the treatment of cutaneous lupus erythematosus (CLE).[18] The nominated bulk drug substance is not a component of an FDA-approved drug product. We evaluated quinacrine 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 quinacrine, safety issues raised by use of this substance in compounding, available evidence of effectiveness or lack of effectiveness, and historical and current use in compounding (Ref. 3).

Quinacrine is well-characterized physically and chemically. Although there are concerns about its safety profile in certain patient populations, we believe these risks are well known within the rheumatology and dermatology specialties that most often treat CLE, and the known risks could be

[15] Specifically, bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate.

[16] FDA requested comments on the proposal to limit listings in this manner in notice of July 31, 2020 (85 FR 46126). 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. The Agency has not finished evaluating the comments received on this proposal, and we intend to take all comments on this issue into consideration in developing our final approach to listing substances on the 503B Bulks List.

[17] In addition to FDA's quinacrine nomination for the 503B Bulks List, the Agency considered data and information from its earlier evaluation regarding the use of this bulk drug substance for the list of bulk drug substances that can be used in compounding under section 503A of the FD&C Act (the 503A Evaluation). See Appendices A–D in ''FDA Memo to File, Clinical Need for Quinacrine Hydrochloride in Compounding Under Section 503B of the FD&C Act'' (Ref. 3). 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 (see Appendix H in Ref. 3).

[18] See Appendix G in Ref. 3.

controlled with appropriate dosing and monitoring. Quinacrine has been used for several decades to treat systemic lupus erythematosus and CLE, and there is a significant body of experience, documented in the scientific literature, that quinacrine may be effective in the treatment of patients with cutaneous lupus, and patients who are not fully clinically responsive to, or are intolerant of, treatment with FDA approved products alone. These patients may respond to the addition of quinacrine to their existing therapy, or to the use of quinacrine alone. On balance, the physical and chemical characterization, safety, effectiveness, and historical and current use of quinacrine weigh in favor of including this substance on the 503B Bulks List. Accordingly, we propose adding quinacrine to the 503B Bulks List for oral use only. We have not identified sufficient evidence to support its use in other routes of administration.

Due to the safety risks referred to above, if quinacrine is placed on the 503B Bulks List, FDA intends to make safety information about the use of quinacrine available to prescribers, pharmacists, outsourcing facilities, and the public through information on FDA's website, in a safety guide, or through other mechanisms, as appropriate.

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

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

The four bulk drug substances that have been evaluated and that FDA is proposing not to place on the list are as follows: Bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate. The reasons for FDA's proposals are included below.

A. Bromfenac Sodium

Bromfenac sodium was nominated in combination with moxifloxacin hydrochloride and prednisolone for inclusion on the 503B Bulks List to compound drug products for postoperative inflammation and pain following cataract surgery.[19] The proposed route of administration is ophthalmic, the proposed dosage forms are an ophthalmic injection [20] and a topical ophthalmic solution,[21] and the proposed compounded product is prednisolone-moxifloxacin-bromfenac (1-0≤.5/0.4 percent). The nominated bulk drug substance, bromfenac sodium, is a component of FDA-approved drug products (*e.g.,* ANDA 203395, NDA 206911, and NDA 203168). FDA has approved bromfenac sodium products as 0.07 percent, 0.075 percent, and 0.09 percent EQ [22] acid ophthalmic solution.[23] [24] The nomination proposes to combine bromfenac sodium with two other bulk drug substances, moxifloxacin hydrochloride and prednisolone, both of which are components of FDA-approved products. Prednisolone acetate [25] is a component of FDA-approved drug products (NDA 017469 and NDA 017011) [26] [27] and is available in a 1 milliliter (mL), 5 mL, 10 mL, and 15 mL suspension containing prednisolone acetate 1.0 percent. Moxifloxacin hydrochloride is a component of FDA-approved drug products (*e.g.,* NDA 021598 and NDA 022428) [28] [29] and is available as an EQ 0.5 percent base ophthalmic solution.

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

The nomination does not identify a medical unsuitability in any of the FDA-approved products that contain bromfenac, prednisolone, or moxifloxacin hydrochloride when these products are administered separately. Instead, it states that the single active-ingredient formulation of these products may make them unsuitable for co-administration after ocular surgeries. Specifically, the nomination states that ''Compounded formulations may alleviate the need for multiple postoperative drops. Topical compounded formulations also may improve patient compliance and alleviate patient confusion because they typically require use of fewer drops.''

However, the labeling for the FDA-approved bromfenac sodium products (*e.g.,* ANDA 203395) specifically warns against the use of bromfenac sodium with topical corticosteroids, which include prednisolone. This is because the use of bromfenac sodium with topical corticosteroids may increase the potential for healing problems.[30] The nomination does not address this warning or provide support for the co-administration of these drug products. We decline to find that the approved drugs are medically unsuitable for some patients because they may be difficult to administer to patients under circumstances that are specifically

[19] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0004. We assume ''bromfenac'' as used in the nomination refers to bromfenac sodium. The nominator did not nominate moxifloxacin hydrochloride or prednisolone separately.

[20] We assume ''injection'' as used in the nomination refers to ophthalmic injection.

[21] The nominator did not specify whether they propose to make an ophthalmic solution or an ophthalmic suspension. We only considered ophthalmic solutions for this review because ''[a]ll drug products containing bromfenac sodium (except ophthalmic solutions)'' is on the list of ''Drug products withdrawn or removed from the market for reasons of safety or effectiveness,'' codified at 21 CFR 216.24 and available at *https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=216.24,* and should not be used in compounding.

[22] EQ refers to the equivalent strength of the active moiety. See *https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.*

[23] See, *e.g.,* ANDA 203395 labeling available as of the date of this notice at *http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/e853723e-8419-4444-89e9-ee3f571b0974/spl-doc.*

[24] See, *e.g.,* NDA 206911 labeling available as the date of this notice at *https://www.accessdata.fda.gov/spl/data/3ae02266-5a0f-4bf2-bc68-ae1c7d2f5239/3ae02266-5a0f-4bf2-bc68-ae1c7d2f5239.xml.*

[25] The nomination did not specify which prednisolone active pharmaceutical ingredient (API) is proposed to be included in their combination. There are several approved ophthalmic formulations of prednisolone acetate or prednisolone sodium phosphate in combination with anti-infectives. The only single ingredient 1% suspension approved for ophthalmic use is prednisolone acetate. It is approved under two separate NDAs, 017469 as OMNIPRED and 017011 as Pred-Forte®. OMNIPRED is available as 5 mL and 10 mL and Pred-Forte® is available in 1 mL, 5 mL, 10 mL, and 15 mL suspension containing prednisolone acetate 1.0%.

[26] See, *e.g.,* NDA 017011 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/3fbf3327-59a2-4e6e-9e43-4f63ea23d54e/3fbf3327-59a2-4e6e-9e43-4f63ea23d54e.xml.*

[27] See, *e.g.,* NDA017469 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/00c60dec-b63c-43ac-9f87-88aeff333136/00c60dec-b63c-43ac-9f87-88aeff333136.xml.*

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

[29] See, *e.g.,* NDA 022428 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/41ea7ffb-02e7-44bd-8ec6-6d4c8e116b99/41ea7ffb-02e7-44bd-8ec6-6d4c8e116b99.xml.*

[30] According to the ''Warnings and Precautions'' section of the FDA-approved labeling for ANDA 203395, ''All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.'' See *http://fdalabel.fda.gov/fdalabel-r/services/spl/set-ids/e853723e-8419-4444-89e9-ee3f571b0974/spl-doc.*

warned against in the approved labeling.

Because co-administration of these products is the subject of a labeled warning, and therefore an inappropriate basis for a finding of clinical need, we do not evaluate the nomination's claims further. However, to help explain our thinking about this nomination and inform public comment, we address the nomination's statement that there is a clinical need to compound a drug containing multiple active ingredients because it may improve patient compliance relative to prescribing FDA-approved drugs that contain a single active ingredient. The nomination does not state that the approved drugs would be medically unsuitable for some patients for the conditions identified in the nomination, and it does not provide data or evidence to support that proposition. Reducing the number of drugs administered for the purpose of convenience is not ''clinical need''; medical unsuitability of the approved drugs is required. While clinical need does not have to be fully established in FDA's analysis of questions 1 and 2, there must be a basis to conclude that such a need may exist before FDA will proceed to the more searching analysis conducted under the balancing test. No such basis is present here.[31]

Accordingly, with respect to the bromfenac sodium drug products proposed to be compounded by the nominator, FDA finds no basis to conclude that there is an attribute of each of the FDA approved drug products that makes each one medically unsuitable to treat certain patients who undergo cataract surgery. There is therefore no attribute of the approved drug products that the proposed compounded drug products are intended to address.

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

Because we have not identified a population for whom the approved products are medically unsuitable for the proposed uses under question 1, we are not considering whether there is a basis to conclude that the drug products proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product under question 2.

3. Additional Comments

For the reasons stated above, we are not evaluating this nomination under the balancing test. However, if this nomination for bromfenac sodium was to proceed to the balancing test, there would be some significant safety and effectiveness concerns to evaluate, which are not addressed in the nomination.

Each of the three ingredients proposed to be used in combination by the nomination is indicated for different medical conditions and has a different FDA-approved dosing regimen: Once daily for bromfenac sodium 0.09 percent,[32] four times daily for prednisolone acetate [33] and three times daily for moxifloxacin hydrochloride.[34] The duration of treatment for each individual drug also differs.

The nomination also describes compounding drug products that include bromfenac sodium in a concentration (EQ 0.4 percent acid) [35] that is more than four times higher than the FDA-approved product (the approved product is available at concentrations of EQ 0.07 percent acid, EQ 0.075 percent acid, and EQ 0.09 percent acid). The nomination does not provide any data or information supporting the need for a higher concentration than the approved drug.

Most of the bulk drug substance nominations FDA has evaluated to date have only proposed to compound drug products containing a single active ingredient. This nomination proposed to compound drug products containing more than one active ingredient. If FDA finalizes its proposal not to include bromfenac sodium on the 503B Bulks List, we intend to remove the substance from Category 1 for purposes of the Interim Policy, which would mean that ophthalmic solutions compounded using the bulk drug substance bromfenac sodium, including the proposed compounded products addressed in this notice, would fall outside the enforcement discretion described in the Interim Policy. We note that FDA's evaluation of bromfenac sodium for inclusion on the 503B Bulks List will not impact FDA's evaluation of any other bulk drug substances for inclusion on the 503B Bulks List, including prednisolone and moxifloxacin hydrochloride, because each bulk drug substance nominated for inclusion on the 503B Bulks List undergoes its own evaluation. We previously proposed not to include moxifloxacin hydrochloride on the 503B Bulks List (85 FR 46126), and we are currently reviewing comments on that nomination. Nominations for prednisolone, if they are not withdrawn, remain the subject of future evaluations. Finally, if FDA determines there is a clinical need for outsourcing facilities to use bulk drug substances to compound the proposed drug products, we would include each substance or combination of substances, as appropriate, on the 503B Bulks List at the time that final determination is made.

B. Mitomycin-C

Mitomycin-C was nominated for inclusion on the 503B Bulks List to compound drug products that treat stomach, pancreas, anal (nonmetastatic), bladder, cervical (recurrent or metastatic), esophageal, gastric, and non-small cell lung cancer.[36] The proposed route of administration is injection and the proposed concentration is 20–40 mg. We evaluated the proposed products for both the intravenous and intravesical routes of administration because the nomination proposed that there is a need for a compounded mitomycin-C drug product for injection and we understand that mitomycin-C is used for both intravesical and intravenous administration in certain oncological conditions. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* ANDA 064144, NDA 022572, and NDA 211728).[37] FDA-approved mitomycin-C

[31] In general, we do not expect to find clinical need for a bulk drug substance to compound drug products containing two or more bulk drug substances unless: (1) Combining the substances is intended to address the medical unsuitability of the FDA-approved drug products for certain patients and (2) the combination is likely to address a clinical need that could not be addressed by delivering each component of the drug product alone. Not including drug products with two or more active ingredients on the 503B Bulks List unless these conditions are met helps to ensure that patients are not exposed to a drug product containing an unnecessary active ingredient, helps avoid risks of unwanted interactions or complications in formulation, and protects the integrity of the drug approval process.

[32] Bromfenac sodium EQ 0.09% acid solution (*e.g.,* ANDA 203395) should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days of the postoperative period.

[33] Two drops topically in the eye(s) four times daily (*e.g.,* NDA 017469).

[34] Instill one drop in the affected eye 3 times a day for 7 days (*e.g.,* NDA 021598).

[35] The nomination states ''0.4%.'' We assume the nominator intended a concentration of EQ 0.4% acid.

[36] See Docket No.FDA–2013–N–1524, document no. FDA–2013–N–1524–2219.

[37] Jelmyto, NDA 211728 was approved on April 15, 2020, as a 40 mg/vial powder for pyelocaliceal administration for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG–UTUC). Jelmyto has not been considered in this memorandum because of the complex nature of the approved product and the fact that there is a more appropriate comparator approved drug product (mitomycin as a 5, 20, and 40 mg vial for solution for intravenous administration). While the nominated dosage form is unclear (''injection''), we assume that the nominator intended to nominate a solution or a powder for solution for intravesical

(*e.g.,* ANDA 064114) is available as a 5, 20, and 40 mg/mL vial for intravenous administration.[38] Mitomycin is also approved as a 0.2 mg vial, which when reconstituted with Sterile Water for Injection, provides a solution for application in glaucoma filtration surgery for use as an adjunct to ab externo glaucoma surgery (*e.g.,* NDA 022572).

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

Regarding the proposed use to treat bladder cancer, the nomination does not explain why an attribute of each of the FDA-approved 5, 20, and 40 mg vials of lyophilized powder for reconstituting into solution is medically unsuitable for the proposed use. For example, if there are patients for whom products for intravenous administration would be medically unsuitable, the nomination does not provide support or explain why the FDA-approved products, or products prepared using the FDA-approved products could not be used for intravesical administration.[39] The nomination states that it may be necessary to compound a mitomycin-C drug product to attain a ''higher, more efficacious dose,'' but the nomination does not identify any specific higher concentrations that the nominator proposes to compound. The approved product is available as a lyophilized powder, which according to the approved labeling, is reconstituted to a final concentration of 0.5 mg/mL or below.[40] While the nomination includes two articles which indicate that there could be a need for a product with a concentration above 0.5 mg/mL,[41] the nomination does not identify an attribute of the FDA-approved products that makes them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address. Further, the nomination proposes to ''include excipients to prevent urine acidification,'' but the nomination does not identify which excipients are proposed for the compounded product, nor does the nomination provide any data or information supporting how the proposed compounded drug products will address that concern.[42]

Regarding the proposed use to treat stomach, pancreas, anal (nonmetastic), cervical (recurrent or metastic), esophageal, gastric, and non-small cell lung cancer, the nomination does not identify an attribute for each FDA-approved product that makes it medically unsuitable to treat certain patients for these conditions and that the proposed compounded products are intended to address.

Accordingly, with respect to the mitomycin 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 for a condition that FDA has identified for evaluation and that the proposed compounded drug products are intended to address.

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

Because the nomination does not identify a population for whom the FDA-approved products are medically unsuitable for the proposed uses, FDA did not consider whether there is a basis to conclude that the drug products proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product under question 2.

C. Nepafenac

Nepafenac was nominated in combination with other bulk drug substances, including prednisolone and gatifloxacin,[43] for inclusion on the 503B Bulks List to compound drug products for ''post cataract surgery ocular complications related to pain, inflammation or bacterial conjunctivitis.'' [44] The proposed route of administration is topical ophthalmic, the proposed dosage forms are a preserved (multidose) and a preservative-free (unit dose) topical ophthalmic suspension, and the proposed compounded products are: (1) ''Nepafenac 0.1%-Prednisolone 1%;'' and (2) ''Nepafenac 0.1%-Prednisolone 1%-Gatifloxacin 0.5%.'' The nominated bulk drug substance, nepafenac, is a component of FDA-approved drug products (*e.g.,* NDA 021862 and NDA 203491).[45] [46] FDA has approved nepafenac as 1.7 mL dropper bottle, and a 4 mL dropper bottle filled with 3 mL sterile ophthalmic suspension containing 0.1 percent (1 mg/mL) nepafenac and as a 4 mL bottle filled with 1.7 mL and 3 mL sterile ophthalmic suspension containing 0.3 percent (3 mg/mL) nepafenac for topical administration.[47] The nomination proposes to combine nepafenac with two other bulk drug substances, prednisolone and gatifloxacin, both of which are components of FDA-approved products. Prednisolone acetate [48] is a component of FDA-approved drug products (NDA 017469 and NDA 017011) and is available in a 1 mL, 5 mL, 10 mL, and 15 mL suspension containing prednisolone acetate 1.0 percent.[49] [50] Gatifloxacin is a

administration (not, as Jelmyto is, a gel for pyelocaliceal administration).

[38] See, *e.g.,* ANDA 064144 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/55ab68d0-c46a-2f41-e054-00144ff88e88/55ab68d0-c46a-2f41-e054-00144ff88e88.xml.* When reconstituted with Sterile Water for Injection, ANDA 064144, and other ANDAs like it, provide a solution for intravenous administration for therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.

[39] In noting this issue, FDA is not suggesting or implying that the approved drug products, or products prepared from them, are approved for the use proposed by the nomination. Mitomycin-C 5, 20, or 40 mg vials of lyophilized powders for solution (for reconstitution) have not been shown to be safe and effective for intravesical administration to treat any condition or disease.

[40] The approved product (*e.g.,* ANDA 064144) is available as a 5, 20, and 40 mg vial of lyophilized powder, which according to the approved labeling, is reconstituted in 10 mL, 40 mL or 80 mL Sterile Water for Injection respectively for intravenous administration.

[41] For example, the nomination cites two articles which used mitomycin administered intravesically for bladder cancer (Refs. 4 and 5). Colombo et al, 2012 administered mitomycin 40 mg in 40 mL saline (1 mg/mL) intravesically to patients and Au et al, 2001 administered mitomycin 40 mg in 20 mL of sterile water (2 mg/mL) or 20 mg in 20 mL of sterile water (1 mg/mL) intravesically to patients (Ref. 4).

[42] The nomination included one article that states, ''[i]n the case of mitomycin C, instability of the drug in acidic urine is an additional problem.'' However, the article does not identify excipients that could be added to intravesically administered mitomycin drug products to address this particular attribute of the approved product. Nor does the article provide data or information to support the need for a compounded drug product containing such excipients. Rather, it discusses administering oral doses of sodium bicarbonate before treatment with an intravesical mitomycin drug product to reduce the acidity of the patient's urine (Ref. 5).

[43] The nominator did not nominate prednisolone or gatifloxacin separately.

[44] See Docket No. FDA–2015–N–3469, document no. FDA–2015–N–3469–0022.

[45] See, *e.g.,* NDA 021862 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021862s017lbl.pdf.*

[46] See, *e.g.,* NDA 203491 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203491s001lbl.pdf.*

[47] See fns. 45 and 46, above.

[48] The nominator did not specify which prednisolone API is proposed to be included in their combinations. There are several approved ophthalmic formulations of prednisolone acetate or prednisolone sodium phosphate in combination with anti-infectives. The only single ingredient 1% suspension approved for ophthalmic use is prednisolone acetate.

[49] See, *e.g.,* NDA 017469 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017469s040lbl.pdf.*

[50] See, *e.g.,* NDA 017011 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/017011s050lbl.pdf.*

component of FDA-approved drug products (*e.g.,* NDA 022548),[51] and is available in a 1 mL or 2.5 mL solution containing gatifloxacin .5 percent.[52]

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

The nomination does not identify a medical unsuitability in any of the FDA-approved products that contain nepafenac, prednisolone, or gatifloxacin when these products are administered separately. Instead, it states that the single active-ingredient formulation of these products may make them unsuitable for co-administration after ocular surgeries. Specifically, the nomination states that ''[a]s a solution, fixed-dosage ophthalmic drug combinations of different pharmacological classes can be efficacious, reduce the side effects of each component and improve patient compliance.'' However, the labeling for the FDA-approved nepafenac products (*e.g.,* NDA 021862 and NDA 203491) specifically warns against the use of nepafenac with topical corticosteroids, which include prednisolone. This is because the use of nepafenac with topical corticosteroids may increase the potential for healing problems. The nomination does not address this warning or provide support for the co-administration of these drug products. We decline to find that the approved drugs are medically unsuitable for some patients because they may be difficult to administer to patients under circumstances that are specifically warned against in the approved labeling.

Because co-administration of these products is the subject of a labeled warning, and therefore an inappropriate basis for a finding of clinical need, we do not evaluate the nomination's claims further. However, to help explain our thinking about this nomination and inform public comment, we address the nomination's statement that there is a clinical need to compound a drug containing multiple active ingredients because it may improve patient compliance relative to prescribing FDA-approved drugs that contain a single active ingredient. The nomination does not state that the approved drugs would be medically unsuitable for some patients for the conditions identified in the nomination, and it does not provide data or evidence to support that proposition. Reducing the number of drugs administered for the purpose of convenience is not ''clinical need''; medical unsuitability of the approved drugs is required. While clinical need does not have to be fully established in FDA's analysis of questions 1 and 2, there must be a basis to conclude that such a need may exist before FDA will proceed to the more searching analysis conducted under the balancing test. No such basis is present here.[53]

Accordingly, with respect to the nepafenac drug products proposed to be compounded by the nominator, FDA finds no basis to conclude that there is an attribute of each of the approved drug products that makes each one medically unsuitable to treat certain patients who undergo cataract surgery. There is therefore no attribute of the approved drug products that the proposed compounded drug products are intended to address.

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

Because the nominator has not identified a population for whom the approved products are medically unsuitable for the proposed uses under question 1, we are not considering whether there is a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product under question 2.

3. Additional Comments

Finally, if this nomination for nepafenac were to proceed to the balancing test, there would be some significant safety and effectiveness concerns to evaluate, which are not addressed in the nomination. Each of the three proposed ingredients intended to be compounded into a single drug product is indicated for different medical conditions and has different FDA-approved dosing regimens: One-time daily for nepafenac,[54] four times daily for prednisolone,[55] and two to eight times daily for gatifloxacin.[56] The duration of treatment for each individual drug also differs, as do the approved indications.

Most of the bulk drug substance nominations FDA has evaluated to date have only proposed to compound drug products containing a single active ingredient. This nomination proposed to compound drug products containing more than one active ingredient. If FDA finalizes its proposal not to include nepafenac on the 503B Bulks List, we intend to remove the substance from Category 1 for purposes of the Interim Policy, which would mean that ophthalmic solutions compounded using the bulk drug substance nepafenac, including the proposed compounded products addressed in this notice, would fall outside the enforcement discretion described in the Interim Policy. We note that FDA's evaluation of nepafenac for inclusion on the 503B Bulks List will not impact FDA's evaluation of any other bulk drug substances for inclusion on the 503B Bulks List, including prednisolone and gatifloxacin, because each bulk drug substance nominated for inclusion on the 503B Bulks List undergoes its own evaluation. Nominations for prednisolone, if they are not withdrawn, remain the subject of future evaluations. Gatifloxacin has not been nominated for inclusion on the 503B Bulks List, and therefore has not been categorized under the Interim Policy; its status under the Interim Policy will not be affected if this proposal is finalized. Finally, if FDA determines there is a clinical need for outsourcing facilities to use bulk drug substances to compound the proposed drug products, we would include each substance or combination of substances, as appropriate, on the 503B Bulks List at the time that final determination is made.

D. Hydroxychloroquine Sulfate

Hydroxychloroquine sulfate was nominated for inclusion on the 503B Bulks List to compound drug products that treat rheumatoid arthritis and juvenile arthritis (also known as juvenile idiopathic arthritis).[57] The proposed route of administration is oral, the proposed dosage forms are a capsule or suspension, and the proposed concentrations are 200–500 mg capsules and 100–200 mg/mL suspension. The nominated bulk drug substance is a component of FDA-approved drug products (*e.g.,* NDA 009768, ANDA

[51] See, *e.g.,* NDA 022548 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022548s002lbl.pdf.*

[52] See fn. 51, above.

[53] See *supra* note 31.

[54] One drop of NDA 021862 0.1% should be applied to the affected eye three times daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. One drop of NDA 203491 0.3% should be applied to the affected eye one time daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

[55] Two drops topically in the eye(s) four times daily.

[56] Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times on Day 1. Days 2 through 7: instill one drop two to four times daily in the affected eye(s) while awake on Days 2 through 7.

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

040104, and ANDA 213342).[58] [59] [60] FDA-approved hydroxychloroquine sulfate is available as 200 mg (equivalent to 155 mg of hydroxychloroquine base), film-coated tablets for oral administration.[61]

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

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.[62] The nomination suggests that the 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 be intended 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 nominator 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.[63]

In addition to the proposed suspension, the nominator also proposes to compound hydroxychloroquine sulfate 200–500 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.

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.

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 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.[64] 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 as the starting material when the compounding process and equipment are appropriately selected. 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. 8).[65] 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.

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 need to include hydroxychloroquine sulfate on the 503B Bulks List under question 2.

V. Conclusion

For the reasons stated above, we tentatively conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substance quinacrine for oral use, and we therefore propose to include it on the 503B Bulks List as described in this notice.

At this time, we find no basis to conclude that there is a clinical need for outsourcing facilities to compound drug products using the bulk drug substances bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate. We therefore propose not to include 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

[58] 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.*

[59] See, *e.g.,* ANDA 040104 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.*

[60] See, *e.g.,* ANDA 213342 labeling available as of the date of this notice at *https://www.accessdata.fda.gov/spl/data/f6b15217-3b65-4d0e-8546-5056d71d525e/f6b15217-3b65-4d0e-8546-5056d71d525e.xml.*

[61] 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.*

[62] 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.

[63] We note that the nominator's proposed concentration of 100–200 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. 6–8), which may be more suitable for the younger pediatric population.

[64] 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.''

[65] 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.

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 Quinacrine Hydrochloride in Compounding Under Section 503B of the FD&C Act,'' January 2021.
4. Colombo, R., L. Rocchini, N. Suardi, F. Benigni, et al., 2012, ''Neoadjuvant Short-Term Intensive Intravesical Mitomycin C Regimen Compared with Weekly Schedule For Low-Grade Recurrent Non-Muscle-Invasive Bladder Cancer: Preliminary Results of a Randomised Phase 2 Study,'' *European Urology,* 62: 797–802.
5. Au, J. L., R. A. Badalament, M. G. Wientjes, D. C. Young, et al., and International Mitomycin-C Consortium, 2001. ''Methods to Improve Efficacy of Intravesical Mitomycin C: Results of a Randomized Phase III Trial,'' *Journal of the National Cancer Institute,* 93: 597–604.
6. 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*.
7. American Society of Hospital Pharmacists (ASHP 2020), '' Hydroxychloroquine Sulfate Suspension 25 mg/mL.'' Retrieved from *www.ashp.org*.
8. 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: March 19, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2021–N–0279]

Determination That Folic Acid, Oral Tablets, 1 Milligram, and Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) has determined that the drug products listed in this document were not withdrawn from sale for reasons of safety or effectiveness. This determination means that FDA will not begin procedures to withdraw approval of abbreviated new drug applications (ANDAs) that refer to these drug products, and it will allow FDA to continue to approve ANDAs that refer to the products as long as they meet relevant legal and regulatory requirements.

FOR FURTHER INFORMATION CONTACT: Stacy Kane, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6236, Silver Spring, MD 20993–0002, 301–796–8363, *Stacy.Kane@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION: In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) (the 1984 amendments), which authorized the approval of duplicate versions of drug products approved under an ANDA procedure. ANDA applicants must, with certain exceptions, show that the drug for which they are seeking approval contains the same active ingredient in the same strength and dosage form as the ''listed drug,'' which is a version of the drug that was previously approved. ANDA applicants do not have to repeat the extensive clinical testing otherwise necessary to gain approval of a new drug application (NDA).

The 1984 amendments include what is now section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), which requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the ''Approved Drug Products with Therapeutic Equivalence Evaluations,'' which is generally known as the ''Orange Book.'' Under FDA regulations, a drug is removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness, or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness (21 CFR 314.162).

Under § 314.161(a) (21 CFR 314.161(a)), the Agency must determine whether a listed drug was withdrawn from sale for reasons of safety or effectiveness: (1) Before an ANDA that refers to that listed drug may be approved, (2) whenever a listed drug is voluntarily withdrawn from sale and ANDAs that refer to the listed drug have been approved, and (3) when a person petitions for such a determination under 21 CFR 10.25(a) and 10.30. Section 314.161(d) provides that if FDA determines that a listed drug was withdrawn from sale for safety or effectiveness reasons, the Agency will initiate proceedings that could result in the withdrawal of approval of the ANDAs that refer to the listed drug.

FDA has become aware that the drug products listed in the table are no longer being marketed.

Application No.	Drug name	Active ingredient(s)	Strength(s)	Dosage form/route	Applicant
NDA 006135	Folic Acid	Folic Acid	1 milligram (mg)	Tablet; Oral	Eli Lilly & Co.
NDA 016131	CLOMID	Clomiphene Citrate	50 mg	Tablet; Oral	Sanofi-Aventis U.S. LLC.
NDA 016419	Propranolol Hydrochloride.	Propanolol Hydrochloride.	1 mg/milliliter (mL)	Injectable; Injection	Baxter Healthcare Corp.
NDA 017473	ORAP	Pimozide	1 mg; 2 mg	Tablet; Oral	Teva Pharms., USA, Inc.
NDA 019916	Morphine Sulfate	Morphine Sulfate	1 mg/mL; 5 mg/mL	Injectable; Injection	ICU Medical, Inc.
NDA 019967	ULTRAVATE	Halobetasol Propionate	0.05%	Cream; Topical	Sun Pharmaceutical Industries, Inc.
NDA 020647	ELDEPRYL	Selegiline Hydrochloride.	5 mg	Capsule; Oral	Somerset Pharms., Inc.
NDA 020925	TAVIST–1	Clemastine Fumarate	1.34 mg	Tablet; Oral	GlaxoSmithKline Consumer Healthcare.