



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

May 24, 2021

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Comments on the Food and Drug Administration’s Notice Proposing Four Exclusions and One Inclusion for the List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act
Docket No. FDA-2018-N-3240**

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments regarding the notice “List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act,” which was published in the *Federal Register* on March 24, 2021 (Docket No. FDA-2018-N-3240).¹

Public Citizen strongly supports the Food and Drug Administration’s (FDA’s) proposal *not* to include bromfenac sodium, mitomycin-C, nepafenac, and hydroxychloroquine sulfate on the list of bulk drug substances for which there is a clinical need under Section 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) (hereafter, the 503B Bulks List). In each case, we agree with the FDA’s analysis and conclusion that the nominated drug should not be included on the 503B Bulks List.

We take no position regarding the FDA’s proposal to include quinacrine hydrochloride on the 503B Bulks List to compound drug products for oral use only.

I. Background

Section 503B of the FDCA, which was enacted under the Drug Quality and Security Act in 2013, stipulates the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the FDCA requirements concerning (a) the approval of drugs under new drug applications or abbreviated new drug applications, (b) the labeling of drugs with adequate directions for use, and (c) drug supply-chain security. Drug products compounded under the conditions in section 503B are not exempt from Current Good Manufacturing Practice requirements and must satisfy other requirements.

¹ 86 FR 15673-15682.

One of the conditions that must be met for a drug product compounded by an outsourcing facility to qualify for exemptions under section 503B is that the outsourcing facility may not compound a drug using a bulk drug substance unless (a) the bulk drug substance appears on the 503B Bulks List or (b) the drug compounded from such bulk drug substances appears on the drug shortage list in effect under section 506E of the FDCA at the time of compounding, distribution, and dispensing.

Previously, the FDA appropriately has noted that compounded drugs pose a higher risk to patients than FDA-approved drugs. The agency once again reaffirmed that position in its March 24, 2021, notice by emphasizing that compounded drugs produced by outsourcing facilities have not undergone FDA premarket review for safety, effectiveness, and quality. In addition, these drugs have not been determined to be safe or effective for conditions of use reflected in drug product labeling and lack a premarket inspection and finding of manufacturing quality. We agree with the FDA that because compounded drug products are subject to a lower regulatory standard than FDA-approved drug products, they should be used only by patients whose medical needs cannot be met by an FDA-approved drug product.

II. Comments about the four nominated bulk drug substances that the FDA proposes to exclude from the 503B Bulks List

Bromfenac sodium and nepafenac

Bromfenac sodium was nominated in combination with moxifloxacin hydrochloride and prednisolone for inclusion on the 503B Bulks List to compound products for postoperative inflammation and pain following cataract surgery; the proposed route of administration was ophthalmic via injection or topical application. Similarly, nepafenac was nominated in combination with other bulk drug substances, including prednisolone and gatifloxacin, for inclusion on the 503B Bulks List to compound drug products for post-cataract surgery ocular complications related to pain, inflammation, or bacterial conjunctivitis; the proposed route of administration was topical ophthalmic.

Importantly, there are FDA-approved formulations of both drugs (as well as the drugs with which they would be combined under the proposed nominations), and the nominations failed to identify a medical unsuitability in any of the FDA-approved products that contain bromfenac, prednisolone, moxifloxacin, nepafenac, or gatifloxacin when these products are administered separately. Moreover, the labeling for FDA-approved bromfenac and nepafenac both specifically warn against the use of these drugs in combination with topical corticosteroids, which include prednisolone, because such combination use may increase the potential for healing problems.

The nominations for bromfenac sodium and nepafenac also failed to (a) state that the FDA-approved formulations of these drugs would be medically unsuitable for some patients for the conditions identified in the nominations and (b) provided data or evidence to support that proposition. We agree with the FDA that reducing the number of drugs administered for the purposes of convenience is not a “clinical need.”

Finally, in the case of both nominations, the FDA noted that each of the three ingredients proposed to be used in combination by the nominations is indicated for different medical conditions and has a different FDA-approved dosing regimen (for example, once daily for bromfenac sodium 0.09 percent, four times daily for prednisolone acetate, and three times daily for moxifloxacin hydrochloride; the duration of treatment for each individual drug also differs). We agree with the FDA that these factors raise significant safety and effectiveness concerns.

We therefore strongly endorse the agency's proposal to exclude bromfenac sodium and nepafenac from the 503B Bulks List.

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. Mitomycin-C is a component of FDA-approved drug products.

The FDA noted that the nomination failed to identify an attribute of the FDA-approved mitomycin-C products that makes them medically unsuitable to treat certain patients for the proposed uses. The FDA therefore appropriately found that there is no basis to conclude that an attribute of the FDA-approved mitomycin-C products makes them medically unsuitable to treat certain patients for a condition that the FDA has identified for evaluation and that the proposed compounded mitomycin-C products are intended to address.

We therefore strongly endorse the agency's proposal to exclude mitomycin-C from the 503B Bulks List.

Hydroxychloroquine sulfate

Hydroxychloroquine sulfate was nominated for inclusion on the 503B Bulks List to compound drug products that treat rheumatoid arthritis and juvenile arthritis. The proposed route of administration is oral, the proposed dosage forms are a capsule or suspension, and the proposed concentrations are 200-500 milligram (mg) capsules and 100-200 mg/milliliter suspension.

The FDA noted that 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. Specifically, the nomination suggested that the approved oral tablets are medically unsuitable in pediatric patients who are unable to swallow tablets. The FDA agreed that there may be certain patients for whom the approved oral tablets are medically unsuitable and that this would depend on a patient's clinical presentation and age, among other considerations. However, the FDA explained that compounded oral suspensions of hydroxychloroquine sulfate can be made from FDA-approved film-coated hydroxychloroquine sulfate tablets.

In addition to the proposed suspension, the nominator also proposed to compound hydroxychloroquine sulfate 200–500 mg capsules for oral administration. The FDA noted that

the nomination did not explain how the proposed compounded capsule products are intended to address the medical unsuitability of the FDA-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 did not identify any data or information as to the need for compounded products with a higher dose than the FDA-approved product. The nomination also claimed that some patients are unable to tolerate excipients in the FDA-approved product, but the nomination did not identify which excipients they were referring to, nor did they provide any data or information supporting how the proposed drug products would address that particular attribute.

The FDA therefore appropriately found that there not 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 therefore strongly endorse the agency's proposal to exclude hydroxychloroquine sulfate from the 503B Bulks List.

In conclusion, to protect public health, we urge the FDA to expeditiously issue a final notice that excludes bromfenac sodium, nepafenac, mitomycin-C, and hydroxychloroquine sulfate from the 503B Bulks List.

III. The FDA needs to rescind its January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act*

It is readily apparent that the basis for nominating the above four bulk drug substances and many other bulk drug substances to the 503B Bulks List was not to ensure that unmet clinical needs are satisfied but rather to meet the commercial goals of the nominators.

There is no dispute that (a) compounded drugs pose a higher risk to patients than FDA-approved drugs; (b) the FDA has evaluated and taken final action on only a small minority of the bulk drug substances nominated for inclusion on the 503B Bulks List; and (c) for every nominated bulk drug substance that the agency has evaluated so far, the agency concluded that the bulk drug substance should not be placed on the 503B Bulks List. Thus, maintaining the FDA's January 2017 *Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act* is indefensible, reckless, and a threat to public health. In particular, it is unacceptable to allow outsourcing facilities to continue compounding drugs using the approximately 250 bulk drug substances that were nominated with sufficient supporting information for the FDA to evaluate them but have not yet either been identified as raising significant safety concerns or been excluded from the 503B Bulks List.

The dangers of the FDA's interim policy to public health are made readily apparent by the nominations of bromfenac sodium and nepafenac. Use of both these drugs in combination with the topical corticosteroids prednisolone, as proposed in the nominations, posed significant health risks to patients following cataract surgery because such combination use may increase the potential for healing problems.

We therefore once again urge the FDA to announce that, within a specified time period (for example, six months), it will rescind its January 2017 interim policy, begin enforcing all requirements of 503B, and not allow outsourcing facilities to produce drugs from bulk drug substances unless those substances appear on either the 503B Bulks List or the agency's drug shortage list.

Thank you for the opportunity to comment on these important public health matters.



Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group