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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
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Comments on the Food and Drug Administration's September 5, 2019, Proposed Rule That Would Amend the List of Bulk Drug Substances That Can be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act Docket No. FDA-2018-N-4845

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments regarding the proposed rule "Amendments to the List of Bulk Drug Substances That Can be Used to Compound Drug Products in Accordance With Section 503A of the Federal Food, Drug, and Cosmetic Act," which was published in the *Federal Register* on September 5, 2019 (Docket No. FDA-2018-N-4845).[1]

In its proposed rule, the Food and Drug Administration (FDA) proposed adding glutaraldehyde, glycolic acid, L-citrulline, pyruvic acid, and trichloroacetic acid (TCA) to the list of bulk drug substances (active pharmaceutical ingredients) that can be used to compound drug products in accordance with certain compounding provisions of the Federal Food, Drug, and Cosmetic Act (FDCA), although they are neither the subject of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph nor components of FDA-approved drugs (hereafter, the 503A Bulks List). Public Citizen supports the addition of glutaraldehyde, glycolic acid, and L-citrulline to the 503A Bulks List, but opposes the addition of pyruvic acid and TCA to the list for the reasons discussed below.

The proposed rule also identified 26 bulk drug substances that the FDA has considered and proposed *not* to include on the 503A Bulks List. Public Citizen strongly supports the exclusion of all 26 of these bulk drug substances from the 503A Bulks List because of concerns regarding the substances' safety or effectiveness.

I. Background

Section 503A of the FDCA stipulates the conditions that must be satisfied for human drug products compounded by a licensed pharmacist or licensed physician to be exempt from

[1] 84 FR 46688-46703.

three sections of the FDCA (sections 501(a)(2)(B), 502(f)(1), and 505 [21 U.S.C. §§ 351(a)(2)(B), 352(f)(1), and 355]). One of these conditions is that a licensed pharmacist in a State-licensed pharmacy or Federal facility or a licensed physician compounds the drug product using bulk drug substances that (1) comply with the standards of an applicable USP or NF monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if such a monograph does not exist, are drug substances that are components of drugs approved by the FDA; or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the FDA, appear on the 503A Bulks List.

Importantly, the FDA previously has noted that compounded drugs pose a higher risk to patients than FDA-approved drugs and that because compounded drug products are subject to lower regulatory standards 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 FDA's proposal to include five bulk drug substances on the 503A Bulks List

In the proposed rule, the FDA proposed adding glutaraldehyde, glycolic acid, L-citrulline, pyruvic acid, and TCA to the 503A Bulks List.

Public Citizen supports the addition of the following bulk drug substances to the 503A Bulks List:

- Glutaraldehyde for topical use at concentrations of 10% or lower, which the FDA evaluated for use in the treatment of warts
- Glycolic acid for topical use at concentrations of 70% or lower, which the FDA evaluated for use in treatment of hyperpigmentation and photodamaged skin
- L-citrulline for oral use, which the FDA evaluated for use in the treatment of certain urea cycle disorders

We agree with the FDA that on balance, the physiochemical characteristics, safety, effectiveness, and historical use of these drugs weigh in favor of inclusion of these three bulk drug substances on the 503A Bulks List. Regarding L-citrulline, we note that the drug has been used clinically in the treatment of certain urea cycle disorders for approximately 30 to 40 years and is considered the standard of care for certain urea cycle disorders.

However, we oppose the inclusion of pyruvic acid for topical use, which the FDA evaluated for use in the treatment of acne, melasma, and warts, on the 503A Bulks List because of the following observations made by FDA reviewers:

- Pyruvic acid is sensitive to sunlight and has been shown to be susceptible to photoinduced oligomerization and decomposition.[2] Therefore, pyruvic acid is unlikely to be stable in ambient environments.

[2] Food and Drug Administration. FDA briefing document for the Pharmacy Compounding Advisory Committee meeting. June 23, 2016. https://www.fda.gov/media/98730/download. Accessed November 25, 2019. PDF page 124.

- The toxicity of pyruvic acid has not been fully evaluated in nonclinical studies, especially after topical administration.[3]
- Topical use of pyruvic acid is associated with local irritation (e.g., burning and erythema), and there have been reports of permanent scarring with topical use of the drug. [4]
- There are no adequate and well-controlled trials evaluating pyruvic acid in the treatment of acne, melasma, or warts. The available information suggests that pyruvic acid may have some efficacy in the treatment of these conditions. However, the limited data are largely from small, open-label trials, allowing only for tentative conclusions regarding efficacy. Moreover, the available data do not suggest an obvious advantage of pyruvic acid over available approved or monographed treatments for acne, melasma, or warts.[5]

We also oppose inclusion of TCA for topical use, which the FDA evaluated for use in the treatment of warts and as a chemical peeling agent, on the 503A Bulks List because of the following observations made by FDA reviewers:

- Clinical data from the use of TCA in the treatment of genital and common warts show that adverse reactions secondary to TCA (concentration 10% to 100%) application included burning, pain, erythema, hyperpigmentation and hypopigmentation. More serious adverse reactions reported were ulcerations, scarring, pustules, punctate keratitis, and conjunctival infection. Adverse events were reported more frequently with higher concentrations.[6]
- Ulcerations were reported in most studies with wart treatment in the genital area. For localized wart involvement, scars or hypopigmentation were the most frequent sequelae. With more extensive genital wart treatment, requirement for suprapubic catheterization has been reported (catheterization reported in the FDA Adverse Event Reporting System and in literature). Also, urinary retention was reported.[7]
- The FDA did not identify any adequate and well-controlled clinical trials evaluating TCA efficacy in the treatment of genital or common warts. The available information suggests that TCA may be efficacious in the treatment of these conditions; however, the limited data are from small, open-label, active controlled trials, or a case report.[8]
- FDA-approved therapies are available to treat genital warts and common warts.[9]
- Even with higher TCA concentrations, current data do not suggest an advantage in efficacy of TCA alone over available approved prescription or over-the-counter treatments for warts.[10]

[3] *Ibid*. PDF page 127.
[4] *Ibid*. PDF page 130.
[5] *Ibid*. PDF page 133.
[6] Food and Drug Administration. FDA briefing document for the Pharmacy Compounding Advisory Committee meeting. November 3, 2016. https://www.fda.gov/media/100283/download. Accessed November 25, 2019. PDF page 66.
[7] *Ibid*. PDF page 66.
[8] *Ibid*. PDF page 70.
[9] *Ibid*. PDF page 66.
[10] *Ibid*. PDF page 70.

III. Comments about the FDA's proposal to exclude 26 bulk drug substances from the 503A Bulks List

The proposed rule identified the following 26 bulk drug substances that the FDA has considered and has proposed *not* to include on the 503A Bulks List:

- 7-keto dehydroepiandrosterone, which the FDA evaluated for use in the treatment of Raynaud's phenomenon and weight loss
- Acetyl-L-carnitine, which the FDA evaluated for use in the treatment of Alzheimer's disease, chemotherapy-induced peripheral neuropathy, and hepatic encephalopathy
- Alanyl-L-glutamine, which the FDA evaluated for use in nutritional support and reducing rates of infectious complications in critically ill and surgical patients
- Aloe vera, 200:1 freeze dried, which the FDA evaluated for use in the treatment of burns, cuts, and wounds
- Artemisinin, which the FDA evaluated for use in the treatment of malaria, helminthic infections, protozoal (particularly toxoplasmosis) infections, stomach ulcers, and cancer
- Astragalus extract 10:1, which the FDA evaluated for use in the treatment of diabetes mellitus, allergic rhinitis, wound healing, asthma, and herpes simplex keratitis
- *Boswellia serrata* extract, which the FDA evaluated for use in the treatment of rheumatoid arthritis and osteoarthritis
- Cesium chloride, which the FDA evaluated for use in the treatment of cancer
- Chondroitin sulfate, which the FDA evaluated for use in the treatment of osteoarthritis
- Chrysin, which the FDA evaluated for use as an aromatase inhibitor
- Curcumin, which the FDA evaluated for use in the treatment of familial adenomatous polyposis, gastric metaplasia, and oral leukoplakia.
- D-ribose, which the FDA evaluated for use in the treatment of heart disease and chronic fatigue syndrome
- Deoxy-D-glucose, which the FDA evaluated for use in the treatment of cancer and herpes simplex virus
- Diindolylmethane, which the FDA evaluated for use in the treatment of cancer
- Domperidone, which the FDA evaluated for use in the treatment of gastroparesis, nausea, and vomiting, and to enhance lactation
- Epigallocatechin gallate, which the FDA evaluated for use in the treatment of obesity, type 1 and type 2 diabetes, cardiac hypertrophy, corneal neovascularization, non-alcoholic fatty liver disease, Parkinson's disease, and wound healing
- Germanium sesquioxide, which the FDA evaluated for use in the treatment of cancer
- Glycyrrhizin, which the FDA evaluated for use in the treatment of hepatitis C by intravenous administration
- Kojic acid, which the FDA evaluated for use in the treatment of melasma and as an iron chelator in wound healing and photodamage prevention
- Nettle, which the FDA evaluated for use in glycemic control
- Nicotinamide adenine dinucleotide, which the FDA evaluated for use in the treatment of fatigue in patients with multiple sclerosis
- Nicotinamide adenine dinucleotide disodium reduced, which the FDA evaluated for use in the treatment of chronic fatigue syndrome

- Rubidium chloride, which the FDA evaluated for use in the treatment of cancer
- Sodium dichloroacetate, which the FDA evaluated for use in the treatment of cancer
- Vanadyl sulfate, which the FDA evaluated for use in the treatment of diabetes, hyperlipidemia, and heart disease, and for the prevention of cancer
- Vasoactive intestinal peptide, which the FDA evaluated for use in the treatment of a condition described as "chronic inflammatory response syndrome"

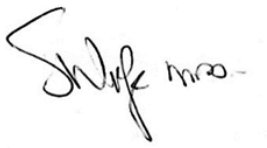
Public Citizen strongly supports the exclusion of all 26 of these bulk drug substances from the 503A Bulks List. We agree with the FDA that on balance, the physiochemical characteristics, safety, effectiveness, and historical use of these drugs weigh against inclusion of these bulk drug substances on the 503A Bulks List. Notably, FDA reviewers raised serious safety concerns about many of these bulk drug substances, including 7-keto dehydroepiandrosterone, acetyl-L-carnitine, alanyl-L-glutamine, aloe vera 200:1 freeze dried, artemisinin, *Boswellia serrata* extract, cesium chloride, chrysin, deoxy-D-glucose, domperidone, epigallocatechin gallate, germanium sesquioxide, glycyrrhizin, rubidium chloride, sodium dichloroacetate, vanadyl sulfate, and vasoactive intestinal peptide. For example, FDA reviewers determined that cesium chloride was unsafe for human use because of the risk of hypokalemia, QT prolongation, life-threatening cardiac arrhythmias, and seizures. For several other of these 26 bulk drug substances, FDA reviewers noted that there was a lack of sufficient data to characterize their safety.

In addition, for most of these 26 bulk drug substances, FDA reviewers noted that there was insufficient evidence to indicate that the bulk drug substances were effective for the evaluated conditions. Also, for nearly all of the diseases and conditions for which these bulk drug substances were evaluated, there are FDA-approved treatments available.

Finally, the FDA recommended or proposed to the Pharmacy Compounding Advisory Committee (PCAC) that each of these 26 bulk drug substances not be included on the 503A Bulks List, and in each case, the PCAC concurred.

Given that the FDA has documented serious safety and effectiveness concerns for these 26 bulk drug substances, the agency's yearslong delays in excluding them from the 503A Bulks List has endangered public health. It is imperative that the FDA act expeditiously to finalize the exclusion of these 26 bulk drug substances from the 503A Bulks List to protect patients.

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



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