

September 17, 2024

VIA E-mail and U.S. Postal Service

Theresa Michele, M.D., Director
Karen Murry, M.D., Deputy Director
Office of Non-Prescription Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, MD 20993

Re: ***Request for information and a meeting regarding status of safety and efficacy testing for three active ingredients deferred from regulation under FDA's 2016 rulemaking on OTC consumer antiseptic washes***; Dockets No. FDA-1975-N-0012, FDA-2015-N-0101, FDA-2016-N-0124

Dear Doctors Michele and Murry:

We write regarding the review by the Food and Drug Administration ("FDA") of the safety and efficacy of benzalkonium chloride (BAC), benzethonium chloride (BZT), and chloroxylenol (PCMX) – active ingredients used in over-the-counter consumer antiseptic washes, which include members of a class of chemicals known as quaternary ammonium compounds ("QACs"). (We refer to these three ingredients as the Deferred antimicrobials.) We request a meeting with you to discuss the status of your review and to share results of our recently published paper regarding the hazards presented by QACs: [Quaternary Ammonium Compounds: A Chemical Class of Emerging Concern](#).¹ The below signed organizations – which have expertise in science policy, public health, environmental health and environmental justice - have a strong interest in FDA expeditiously completing its review of the Deferred antimicrobials, which our research indicates may be linked to health hazards. In addition, we ask that you post to the rulemaking docket any studies, correspondence, comments or materials of any type related to your review of the Deferred antimicrobials that are not already posted. We also ask that you add this letter to the relevant rulemaking dockets.

Context and Background: In September 2016, FDA finalized a rule establishing that 19 specific active antimicrobial ingredients are not Generally Recognized as Safe ("GRAS") and not Generally Recognized as Effective ("GRAE") for use as a consumer antiseptic wash, and therefore over-the-counter ("OTC") consumer antiseptic wash drug products containing these active

¹ Environmental science & technology, 57(20), 7645–7665.
<https://pubs.acs.org/doi/10.1021/acs.est.2c08244>.

ingredients are misbranded (“2016 Final Rule”).² FDA’s conclusion that these ingredients are not GRAE was based on the determination that no data “demonstrate that there is any additional benefit from the use of these active ingredients in consumer antiseptic wash products compared to nonantibacterial soap and water.”³ FDA’s conclusion that these ingredients are not GRAS was based on its determination that their use could impact development of bacterial resistance,⁴ and at least some of the ingredients are linked to adverse health effects in toxicological studies and/or have data gaps related to health effects that undermine a GRAS determination.⁵

However, the 2016 Final Rule deferred a decision for one year on whether BAC, BZT and PCMX are GRAS/GRAE when used in over-the-counter consumer antiseptic washes. This was done in response to a request from manufacturers and a trade association for more time to conduct the studies that FDA required to comport with the safety and efficacy testing requirements of 21 C.F.R. section 330.10.⁶ FDA then extended the 2016 deferral several times to accommodate the manufacturers’ repeated requests. The deferrals have been granted with the assumption that the manufacturers are performing the required studies regarding safety and effectiveness of the Deferred antimicrobials and will be providing regular progress reports. Based on relevant rulemaking dockets,⁷ it appears that the last manufacturers’ report to FDA on the progress of their studies was on July 14, 2020.⁸ According to FDA’s November 2020 response, some required studies had still not been performed; FDA asked for an updated report by October 1, 2021.⁹ The rulemaking docket includes an October 2021 entry entitled “Slides from GOJO meeting with FDA re: Hand Sanitizer Concerns on October 4, 2021,” but the entry is

² [Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use](#), 81 Fed. Reg. 61,106 (Sept. 6, 2016). The 19 specific ingredients are listed in the Final Rule at 81 Fed. Reg. 61,125.

³ 81 Fed. Reg. at 61,107.

⁴ 81 Fed. Reg. at 61,113-14.

⁵ 81 Fed. Reg. at 61,119-124.

⁶ <https://www.regulations.gov/document/FDA-1975-N-0012-0640>.

⁷ It is not clear which rulemaking docket covers the deferred decision on BAC, BZT and PCMX. The 2016 Final Rule was included in Docket FDA-1975-N-0012, but that docket is now listed as “closed.” FDA’s November 18, 2020 letter to The American Cleaning Institute regarding testing of the Deferred antimicrobials references three docket numbers: FDA-1975-N-0012; FDA-2015-N-0101; and FDA-2016-N-0124. However, it is not clear if FDA-2015-N-0101; and FDA-2016-N-0124 cover consumer antiseptic washes.

⁸ <https://www.regulations.gov/document/FDA-2016-N-0124-0409>. This report was posted to the docket on December 4, 2020.

⁹ <https://www.regulations.gov/document/FDA-2016-N-0124-0407>.

marked “Restricted: Confidential Business Information.”¹⁰ No later documents have been posted to the docket.

Although FDA’s November 18, 2020 states that the GRAS and GRAE status of BAC, BZT and PCMX is still undecided, and will depend on the analysis of the required studies of their safety and effectiveness, the Spring 2024 Regulatory Agenda for the U.S. Department of Health and Human Services/Food and Drug Administration makes no reference to a rulemaking on over-the-counter consumer antiseptic washes.

Concerns: We are concerned that QACs continue to be widely used in over-the-counter consumer antiseptic washes, *including by children* (many of whom use antiseptic washes daily – at home and in school) – despite the absence of data that they are GRAE or GRAS, and in the absence of FDA performing a “benefit-to-risk ratio” analysis to assess whether any benefit outweighs the health concerns, which is required by FDA’s rules.¹¹ Questions about whether BAC, BZT and PCMX provide any antiseptic benefit loom large especially since the other 19 antimicrobials that were part of the 2016 Final Rule were found to be no more effective than non-antimicrobial soap and water. Meanwhile, the evidence of the health hazards linked to QACs including their possible contribution to antimicrobial resistance has only gotten stronger.¹² The fact that neither the safety nor the efficacy of the Deferred antimicrobials has been established in the 8 years that FDA has already given the manufacturers may be indication that they are neither safe nor effective.

Request for Information:

The public trusts the FDA to ensure that products such as consumer antiseptic washes are safe (both in terms of antibacterial resistance and toxicology) and also effective. We would appreciate your meeting with us (via zoom) to discuss the status of industry and other scientific studies and the progress of your regulatory review. In addition, we ask that you update the rulemaking docket by: 1) adding any studies, correspondence, comments or materials of any type related to the Deferred antimicrobials that is not already posted; and 2) adding a version of the Slides from GOJO meeting with FDA re: Hand Sanitizer Concerns on 4 October 2021 that redacts only the confidential material. We question that every word on every slide truly warrants confidential business information protection.

¹⁰ <https://www.regulations.gov/comment/FDA-2016-N-0124-0255>.

¹¹ 21 C.F.R. section 330.10(a)(4)(iii).

¹² See Arnold, W. A., Blum, A., Branyan, J., Bruton, T. A., Carignan, C. C., Cortopassi, G., Datta, S., DeWitt, J., Doherty, A. C., Halden, R. U., Harari, H., Hartmann, E. M., Hrubec, T. C., Iyer, S., Kwiatkowski, C. F., LaPier, J., Li, D., Li, L., Muñiz Ortiz, J. G., Salamova, A., ... Zheng, G. (2023). Quaternary Ammonium Compounds: A Chemical Class of Emerging Concern. *Environmental science & technology*, 57(20), 7645–7665. <https://doi.org/10.1021/acs.est.2c08244>.

We are grateful for your work to ensure the safety and efficacy of over-the-counter consumer antiseptic washes, and very much appreciate your insistence that GRAS/E determinations for these products must be supported by strong science. We look forward to meeting with you to discuss the status of this rulemaking. We also appreciate your updating the docket as soon as possible, and ask that you provide us with email notice once the docket is updated. We also ask that this letter be posted to all relevant rulemaking dockets. Please contact Anna Soehl at Green Science Policy Institute (Anna@GreenSciencePolicy.org) to arrange a zoom meeting.

Thank you for your consideration.

Sincerely,
Arlene Blum
Executive Director, Green Science Policy Institute

Eve Gartner
Director, Crosscutting Toxics Strategies, Earthjustice

Alaska Community Action on Toxics
Alliance of Nurses for Healthy Environments
Breast Cancer Prevention Partners
Brighter Beginnings Administration
Bringing Back the Natives Garden Tour
Buxmont Coalition for Safer Water
California Brain Tumor Association
California Nurses for Environmental Health and Justice
Center for Community Action and Environmental Justice
Center for Environmental Health
Clean Water Action
CleanEarth4Kids.org
Consumer Reports
Ecological Options Network
Ecology Center
Environmental Working Group
Families Advocating for Chemical and Toxics Safety
GMOScience
Grassroots Environmental Education
Indivisible CA Green Team
Learning Disabilities Association of America
Long Beach Gray Panthers
Mamavation

Massachusetts Breast Cancer Coalition
Maternal and Child Health Access
Nantucket PFAS action group
National Stewardship Action Council
Non Toxic Communities
Non-Toxic Neighborhoods
Natural Resources Defense Council
Pesticide Free Zone
Protect Wild Petaluma
Public Employees for Environmental Responsibility
Retired National Education Association
Safer Made Ventures
San Francisco Firefighters Cancer Prevention Foundation
Science and Environmental Health Network
SoCoCAN!
The Defend Them All Foundation
Toxic Free NC
Wholly H2O
Women's Voices for the Earth