July 5, 2018

American Cleaning Institute  
Attention: Mr. Richard Sedlak  
Executive Vice President, Technical and International Affairs  
1331 L Street, NW  
Suite 650  
Washington, D.C. 20005

Dear Mr. Sedlak:

Please refer to your April 12, 2018, submission to docket FDA-2015-N-0101-1451, with reference to docket FDA-1975-N-0012 Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record, FDA-2015-N-0101 Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record, and FDA-2016-N-0124 Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record, which contained the final report for a time-kill study titled: An In Vitro Time-Kill Evaluation of Four Test Materials When Challenged with Various Bacterial and Yeast Species. The four test materials evaluated include benzalkonium chloride (BAC), benzethonium chloride (BZC), Dettol (chloroxylenol, PCMX), and ethanol (EtOH).

We note that you also evaluated organisms in food handler settings, and you anticipate that these data will satisfy the need for time-kill data for BAC, BZC, PCMX, and EtOH under a future food handler antiseptic rule. The Agency has not yet issued a proposed rule or monograph on proposed conditions under which OTC antiseptics for use by the food industry are generally recognized as safe and effective. Accordingly, we cannot concur with your assessment with respect to food handler antiseptics at this time.

Our review of the time-kill final report for BAC, BZC, PCMX, and EtOH for health care and consumer antiseptics is complete. See our comments below:
Test materials

1. We note that the eligible monograph concentration range for the four active ingredients for the indications of consumer wash, consumer rub, and health care antiseptics is as follows:

- Benzalkonium chloride 0.1-0.13% (56 FR 33644 at 33663 and 33677)
- Benzethonium chloride 0.1-0.2% (56 FR 33644 at 33677)
- Chloroxylenol (PCMX) 0.24-3.75% (59 FR 31415 at 31415)
- Ethanol (alcohol) 60-95% (59 FR 31415 at 31436)

To maintain the monograph concentration range claim for the above indications we expect that evidence of each active ingredient’s efficacy throughout the corresponding monograph concentration eligible range be demonstrated by the required efficacy studies as specified for the indications of consumer wash, consumer rub, and health care antiseptics. In the case of the consumer wash ingredients, which have clinical outcome testing requirements, in vitro effectiveness testing may be sufficient to address the range of concentrations claimed, in addition to clinical outcome effectiveness testing; i.e., we expect the active ingredient in the clinical outcome study to be evaluated at a unique concentration (in the lower end of the claimed range), and additional in vitro effectiveness testing to be performed throughout the claimed eligible monograph concentration range.

2. For the health care and consumer antiseptic deferred active ingredients, it is our expectation that the time-kill assay demonstrates the lack of bactericidal activity of the vehicle within the chosen contact time. However, test materials #1 (BAC) and 2 (BZC) are tested in the presence of 1% propylene glycol (v/v), and a vehicle arm (e.g., 1% propylene glycol) are not included in the study. We note that bactericidal activity of propylene glycol has been previously described. Provide rationale on the use of 1% propylene glycol in the BAC and BZC solutions for test materials #1 and 2 and provide data or publications to justify and support that, at the concentration used, propylene glycol does not contribute to the bactericidal activities of BAC and BZC demonstrated in the report.

Equally, the bactericidal activity of chloroxylenol, test material #3, was demonstrated in the final formulated product, Dettol, and a vehicle arm was not included in the study. Provide rationale on the lack of vehicle arm and provide data or publications to demonstrate that the composition of the vehicle does not contribute to the bactericidal activity of Dettol presented in the report.

Neutralization validation

3. In the June 17, 2016, Advice Letter, the Agency recommended that you perform the following tests in the neutralization validation study: neutralizer effectiveness (Test A), neutralizer toxicity (Test B), test organism viability control (Test C), and test material control (Test D). However, it appears that Test D

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2. Nalawade et al., 2015; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4415329/
was excluded from the neutralization validation study. Conduct a study for Test D or provide adequate justification for not conducting Test D.

4. The exposure time for \textit{E. coli} and \textit{S. aureus} was $\geq 15$ minutes, while for \textit{S. pneumoniae} and \textit{B. fragilis}, there was no hold time. Provide justification for the discrepancy in the hold time.

Other

5. In the Final Report’s Executive Summary, you stated that the “antimicrobial efficacy of each test material is summarized in terms of the total number and types of strains for which total inactivation to the limit of detection was achieved”. Specify the limit of detection for total inactivation in the time-kill study.

If you have any questions, call Celia Peacock, Regulatory Project Manager at (301) 796-4154.

Sincerely,

Theresa Michele, MD
Director
Division of Nonprescription Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research