Docket No FDA-1975-N-0012
Docket No FDA-2015-N-0101
Docket No FDA-2016-N-0124

MEETING REQUEST-
WRITTEN RESPONSES

The American Cleaning Institute
Attention: James Kim, PhD
Vice President, Science and Regulatory Affairs
1401 H Street, N.W.
Suite 700
Washington, D.C. 20005

Dear Dr. Kim:[1]

Please refer to Docket No FDA-1975-N-0012, Docket No FDA-2015-N-0101, and Docket No FDA-2016-N-0124 for benzalkonium chloride.

We also refer to your June 10, 2020 correspondence, containing a meeting request. The purpose of the requested meeting was to discuss in vivo efficacy studies for benzethonium chloride for use as a healthcare antiseptic.

Further reference is made to our Meeting Granted letter dated July 6, 2020, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 10, 2020 background package.

If you have any questions, call Kris Leazer, Regulatory Project Manager at (240) 402-1418.

Sincerely,

Francis E. Becker -S

Digitally signed by Francis E. Becker -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13004312 06, cn=Francis E. Becker -S
Date: 2020.09.29 15:50:09 -04'00'

Francis Becker, MD, FACP
Director
Division of Nonprescription Drug Products II
Office of Nonprescription Drugs
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[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Enclosure:

- Written Responses

WRITTEN RESPONSES

Meeting Type:	Type C
Meeting Category:	Guidance
Application Number:	Docket No FDA-1975-N-0012 Docket No FDA-2015-N-0101 Docket No FDA-2016-N-0124
Product Name:	health care antiseptic washes (benzethonium chloride)
Indication:	topical antiseptic
Sponsor Name:	The American Cleaning Institute

BACKGROUND

American Cleaning Institute (ACI) and its members, Henkel Corporation, Lonza Inc, and Georgia Pacific, have requested a type C Written Response Only meeting with FDA in order to obtain feedback on benzethonium chloride (BZT) specifically related to health care antiseptic indications. In response to ACI's March 12, 2019 progress report, FDA issued a deferral letter (August 14, 2019) noting missing status and milestones for some of the in vivo efficacy studies for certain health care antiseptic indications. FDA also requested to meet with ACI to discuss these issues in more detail.

The Sponsor's questions are **bolded**; FDA's General Comments and Responses are *italicized*.

FDA General Comments

Section 505G of the Federal Food, Drug & Cosmetic Act (FD&C Act or Act), as added by the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), enacted on March 27, 2020, addresses nonprescription drugs marketed without an approved application. The CARES Act replaces the rulemaking process that was previously used in determining the conditions under which certain nonprescription drugs are generally recognized as safe and effective (GRASE) with a streamlined administrative order process.

Under 505G(a)(3) of the FD&C Act, as added by the CARES Act, drugs that were classified as Category III in a tentative final monograph (TFM) that is the most recently applicable proposal or determination for such drug issued under 21 CFR Part 330 – and

that were not classified in such a TFM as Category II for safety or effectiveness – are not required to have an approved application under section 505 in order to be marketed, as long as they are in conformity with the relevant conditions of use outlined in the applicable TFM, including the active ingredient, and comply with all other applicable requirements. Health care antiseptics were addressed in the TFM entitled "Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products," Proposed Rule, 59 FR 31402 (June 17, 1994) (1994 TFM), as further amended by the "Safety and Effectiveness of Health Care Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; and Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record," and Proposed Rule, 80 FR 25166 (May 1, 2015) (Health Care Antiseptics Proposed Rule). In the Health Care Antiseptics Proposed Rule, which was the most recently applicable proposal or determination for such drugs issued under 21 CFR Part 330, health care personnel hand washes containing BZT as an active ingredient were classified in Category III. Accordingly, nonprescription health care personnel hand wash products containing BZT as an active ingredient can currently be legally marketed if they are in conformity with the conditions of use in the TFM, as amended by the Health Care Antiseptics Proposed Rule, and comply with all other applicable requirements.

While, as a result of the CARES Act, nonprescription health care personnel hand wash products containing BZT as an active ingredient have legal marketing status as described above, FDA continues to believe that completion of the studies necessary to demonstrate the safety and effectiveness of BZT for use as an active ingredient in health care personnel hand wash is important for the public health. We are committed to working with you to fill the remaining data gaps. As we explain in detail below, FDA has reviewed the information that ACI has submitted thus far in support of its progress to demonstrate safety and effectiveness of health care personnel hand washes containing BZT as an active ingredient, and we believe that ACI continues to demonstrate its ongoing commitment to and progress in conducting the necessary safety and efficacy studies. We, therefore, do not intend to issue a proposed administrative order regarding the safety and effectiveness of health care personnel hand washes that contain BZT as an active ingredient for one year from the issuance of this letter, subject to renewal. An updated report that includes a description of ACI's specific progress for this active ingredient for this use should be submitted to FDA by August 1, 2021.

1.0 QUESTIONS AND RESPONSES

<u>Question 1</u>: Does FDA agree that the proposed testing plan of BZT for 2020 and 2021 is adequate to continue to secure deferral for benzethonium chloride for health care antiseptics?

FDA Response to Question 1:

We understand your proposed testing plan of BZT to include: 1) initiating bioanalytical method development for the MUsT in 3Q 2020; and 2) conducting the pilot MUsT for BZT in Q12021 after completing the pivotal MUsT for benzalkonium chloride (BAC).

We note that in response to your progress report dated March 12, 2019, we issued a deferral letter dated August 14, 2019. The deferral letter noted that work related to BZT was missing the status and milestones for in vivo efficacy studies for the health care personnel hand wash indication. We also requested to meet with you to discuss these issues in more detail. We note that your progress report dated July 14, 2020 and this briefing package include BZT in vivo efficacy study plans for the health care personnel hand wash indication. To date, you have provided periodic reports demonstrating your commitment to and ongoing progress in conducting the necessary safety and efficacy studies to address existing data gaps, including the information summarized below:

Effectiveness In Vitro Studies

(1) *The Minimum Inhibitory Concentration (MIC) and Minimum Bacterial Concentrations (MBC) studies for BZT are complete (FDA's Advice letter dated August 29, 2019).*

(2) *The Time-kill studies for BZT are also complete (FDA's Advice Letter dated August 9, 2019).*

Nonclinical Safety (Antibiotic Resistance)

(3) *According to the BZT Timeline for Completion, the literature review has been completed and a final report will be submitted in the 4th quarter of 2020.*

Safety (MUsT)

(4) *Determination of frequency and duration of dosing: An electronic surveillance study was initiated in 2017 with the primary objective of learning the hand hygiene practices for health care workers. This information will be used to define the number of hand hygiene events in a pilot MUsT for health care antiseptic products containing BZT.*

(5) *Determination of composition of tested formulations: A final report for in vitro dermal penetration (IVDP) studies of BZT with human skin was submitted to FDA for a May 9, 2018 Feedback Meeting. Based on the submitted IVDP data, you plan to select the formulation with the highest penetration to support both consumer and health care uses in the pilot MUsT.*

(6) *Pilot MUsT: In anticipation of the pilot BZT MUsT, you plan to initiate validation work for the detection of BZT in plasma and urine. You also plan to submit a protocol for the pilot BZT MUsT study, allowing adequate time for our review and comments, prior to study initiation. Based on the completed IVDP work, the formula with the highest penetration for BZT will be selected for the pilot study (see response to question 2).*

Effectiveness In Vivo Studies

(7) *Health care personnel hand wash: Pivotal health care personnel hand wash studies may be conducted along with benzalkonium chloride, chloroxylenol, and povidone-iodine active ingredients without performing a pilot study for BZT. In 2019, two potential laboratories were identified and are conducting pilot studies to develop their proficiency in in vivo efficacy study methods. Further qualification activities have been delayed due to laboratory closures and travel restrictions as a result of the COVID-19 pandemic. Training at each laboratory will resume once operations allow.*

Based on our review of the submission, we believe that you continue to demonstrate an ongoing commitment to and progress in conducting the necessary safety and efficacy studies to address existing data gaps for BZT and the health care personnel hand wash indication.

As explained above, we do not intend to issue a proposed order regarding the safety and effectiveness of health care personnel hand washes that contain BZT as an active ingredient for one year, subject to renewal. Submit an updated report that includes a description of your specific progress for this active ingredient for this use by August 1, 2021.

Question 2: Does FDA agree that testing the antibacterial formulation with the highest penetration of BZT (0.2%) from the IVDP study should suffice for the pilot MUsT for healthcare handwash application?

FDA Response to Question 2:

No, we do not agree. We acknowledge your IVDP study report submitted in 2018. However, the study included only two formulations containing BZT. Given at least two possible dosage forms (foaming and liquid) and a number of possible formulations that could be formulated with BZT, selecting a formulation which resulted in a higher penetration from two formulations does not provide adequate scientific justification that the selected formulation represents the one with the highest dermal absorption potential. Thus, we recommend conducting the IVDP study with at least four formulations, including at least one formulation containing a permeation enhancer.

These additional formulations do not need to be currently marketed formulations, but should, as outlined in the MUsT Guidance be "market image" formulations. For additional information, refer to the FDA guidance for industry, Maximal Usage Trials for Topically Applied Active Ingredients Being Considered for Inclusion in an Over-The-Counter Monograph: Study Elements and Considerations (May 2019) https://www.fda.gov/media/125080/download .

We also do not agree with your claim that 30 hand washes per day represents maximal use conditions in the health care setting. You will need to provide adequate justification for the proposed dosing frequency and the treatment duration in the MUsT program based on literature or observational studies appropriate for the healthcare hand wash indication. We note that the industry conducted two observational studies of hand washing in childcare facilities suggesting ~40 hand washes per 8-hour period would reflect maximal use conditions of consumer hand wash products. However, compared to childcare workers, health care workers presumably wash hands more frequently during the same period and they may work longer per day (e.g., 12 hours a day as night shift hours). If you anticipate that frequent hand washes by using products containing BZT could cause skin irritation in subjects in the MUsT program, we recommend providing a specific, neutral moisturizer to all subjects to be used 1 to 2 hours after the last hand wash of the day (not during dosing phase) to relieve irritation and improve subject compliance. Such moisturizers are not to be used in the morning prior to dosing.

Question 3: If the agency does not agree with the proposed testing plan, what additional steps or timing would satisfy the securing of a deferral for the following indications?

FDA Response to Question 3:

See our responses to Questions 1 and 2.