DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

March 10, 2016

Docket No. FDA-1975-N-0012

Lonza America, Inc.
Attention: Michael R. Neilson
Assistant General Counsel
90 Boroline Road
Allendale, NJ 07401

American Cleaning Institute
Attention: Richard Sedlak
Executive Vice President
Technical & International Affairs
1331 L Street, NW, Suite 650
Washington, DC 20005

Henkel North America
Attention: Elizabeth Dail
Director of Product Safety, Regulatory Affairs
Clinical Testing, Microbiology and Analytical
One Henkel Way
Rocky Hill, CT 06067-3901

Dear Mr. Neilson, Mr. Sedlak, and Ms. Dail:

In December 2013, FDA issued a proposed rule (PR) under the OTC drug review on consumer antiseptic washes (2013 PR; 78 FR 76444). FDA proposed testing requirements, including nonclinical and clinical safety studies, and clinical outcome studies, for establishing that active ingredients used in consumer antiseptic products intended for use with water ("Consumer Antiseptic Washes") are generally recognized as safe and effective (GRAS/E).

FDA held a public meeting with the American Cleaning Institute (ACI) and other attendees on March 20, 2015, and with Lonza America, Inc., (Lonza) and other attendees, including Henkel North America, on May 6, 2015, to discuss the proposed protocols for studies to fill the safety and efficacy data gaps identified in the 2013 PR for benzalkonium chloride and benzethonium chloride. Briefing packages and

minutes for these meetings are available in the public docket referenced above (http://www.regulations.gov/#!searchResults;rpp=25;po=0;s=FDA-1975-N-0012;fp=true;ns=true).

It is our understanding that Lonza and ACI request that benzethonium chloride be deferred from inclusion in the final rulemaking to allow more time for completion of studies necessary to fill the data gaps identified in the 2013 PR. Such studies are intended to improve understanding of the characteristics of this ingredient that may affect safety and efficacy and would therefore better inform FDA's GRAS/E determination. Accordingly, FDA is prepared to initially defer this ingredient from rulemaking for one year, subject to renewal, to permit these studies to be conducted; however, if no such studies have been commenced, or if the studies in progress do not appear, in FDA's judgment, to be productive, the agency expects that it will proceed to rulemaking for this ingredient after this initial deferral. To facilitate deferral, we request that you submit clear statements of your intent to conduct all necessary studies with proposed timelines, as described in this letter, and submit full study reports to the public docket. Further detail on the necessary studies, including FDA's guidance on study objectives and design, follows below.

Studies Necessary to Support a "Generally Recognized as Safe and Effective" Determination

As described in the 2013 PR, the following studies are needed to determine if benzethonium chloride is GRAS/E for use in consumer antiseptic wash products.[1] We have considered the various submissions and meeting discussions noted above and have identified the remaining outstanding data requirements to support a GRAS/E determination for benzethonium chloride to be used in a consumer antiseptic wash products.

To maximize the utility of the study data, FDA strongly recommends that you submit protocols for each of the studies described below for FDA review and comment prior to initiation of the studies. To ensure timely review of your protocols by FDA, copy the Division of Nonprescription Drug Products (DNDP) on your submissions to the docket.

Safety Studies

1. Nonclinical (Animal) Studies

   A. Oral carcinogenicity study[2]
   Oral carcinogenicity safety testing is required to determine that benzethonium chloride is Generally Recognized as Safe (GRAS). As discussed in the May 6, 2015 meeting, the need for an oral carcinogenicity study to fill the carcinogenicity data gap will depend on the results of a human pharmacokinetic maximal use trial (MUsT). Before conducting an oral carcinogenicity study, the protocol will need to be submitted, reviewed and accepted by CDER's Carcinogenicity Assessment Committee.

   For further guidance, see the following link for " Memorandum of Meeting Minutes from FDA CDER to Lonza America, Inc."
   http://www.regulations.gov/#!documentDetail;D=FDA-1975-N-0012-0634

   Also see the link for FDA's Guidance for Industry Carcinogenicity Study Protocol

[1] 78 FR 76444, 76465.
[2] Id.

Submissions
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078924.pdf.

B. ADME studies[3]

Oral and dermal exposure data (absorption, distribution, metabolism, and excretion), that allow for a comparison of exposures achieved in toxicity studies to those achieved in humans after maximal use, are required for a determination that benzethonium chloride is GRAS. It is acceptable that oral exposure data be collected during the oral carcinogenicity study, if conducted.

For further guidance, see the link for FDA's Guideline for Industry Toxicokinetics: The Assessment of Systemic Exposure in Toxicology Studies
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074937.pdf

C. Developmental and Reproductive Toxicity (DART) testing[4]

The need to conduct further DART testing will depend on the extent of dermal absorption obtained from a MUsT. Studies to assess the fertility and pre/postnatal toxicity may be waived if a human MUsT shows low levels of dermal absorption and if no additional safety signals were obtained from the pending toxicological testing program (e.g. oral carcinogenicity).

D. Hormonal effects study[5]

It is possible that DART and carcinogenicity studies conducted with appropriate endpoints may suffice to address adverse effects related to hormonal activity for benzethonium chloride. Alternatively, a separate study may be conducted.

2. Maximal Use Trial (MUsT)[6]

To maximize the utility of the MUsT data, FDA recommends initiating dosing in the MUsT within one year of the receipt of this letter, and submitting the full report of the MUsT as soon as practicable after its completion.

Study Objective: Human pharmacokinetic study to determine dermal absorption when applied topically to subjects with healthy skin under maximal use conditions, including documentation of validation of the methods used to measure benzethonium chloride and its metabolites.

Note that discussions of a proposed protocol for a MUsT of benzethonium chloride have occurred via public communication including an advice letter from FDA providing comments on a

[3] Also referred to as an ADME study (see 78 FR 76444, 76455), referenced as necessary for this ingredient at 76465.
[4] 78 FR 76444, 76465.
[5] Id.
[6] 78 FR 76444, 76463.

proposed MUsT protocol. These communications describe the necessary design elements that a MUsT protocol would contain in order to study the maximal use of benzethonium chloride. For further guidance, see the following link for " Advice letter from FDA CDER to Lewis & Harrison" http://www.regulations.gov/#!documentDetail;D=FDA-1975-N-0012-0635.

Efficacy Studies[7]

1. In vitro time- kill assay[8]

Conduct a modified time-kill assay using the reference strains listed below, as well as 25 clinical isolates for each of the listed reference strains. The active ingredient will be considered bactericidal at the concentration and contact time in which it demonstrates a reduction of viable bacteria of $3\log_{10}$ or greater.

- *Enterococcus faecalis* (ATCC 19433 and ATCC 29212)
- *Staphylococcus aureus* (ATCC 6538 and ATCC 29213) and methicillin-resistant *S. aureus* (MRSA) (ATCC 33591 and ATCC 33592)
- *Streptococcus pyogenes* (ATCC 14289 and ATCC 19615)
- *Listeria monocytogenes* (ATCC 7644 and ATCC 19115)
- *Campylobacter jejuni* (ATCC 33291 and ATCC 49943)
- *Escherichia coli* (ATCC 11775 and ATCC 25922)
- *Pseudomonas aeruginosa* (ATCC 15442 and ATCC 27853)
- *Salmonella enterica Serovar Enteritidis* (ATCC 13076) and *Serovar Typhimurium* (ATCC 14028)
- *Shigella sonnei* (ATCC 9290 and ATCC 25931)

2. Clinical Outcome Study[9]

Consider the recommendations provided below in designing the clinical outcome study:

Study Objective: Demonstrate the contribution of benzethonium chloride in the prevention of disease occurrence.

Study Design: Randomized, double blind, parallel, 2-arm, vehicle-controlled.

Subjects: Individual healthy male and nonpregnant female subjects of any age who are able to wash their hands with a consumer wash with water OR households with at least one preschool-age child. [10]

---

[7] See 78 FR 76444.
[8] Id. at 76453.
[9] Id. at 76452.
[10] "While the role of personal hygiene in reducing infections has been demonstrated in specific groups (for example, persons with dermatologic problems, hospitalized patients, or person in developing countries with suboptimal hygiene or public services), there is a paucity of data to demonstrate an advantage of antibacterial soaps for the general, healthy public" per Larson EL et al. Effect of antibacterial home cleaning and handwashing products on infectious disease symptoms: a randomized double-blind trial. *Ann Intern Med.* 2004 Mar 2: 140 (5): 321, 326.

A. We recommend conducting a prevention of disease occurrence clinical outcome study in a community setting comparing the test consumer antiseptic handwash drug product and water versus vehicle (i.e., the test consumer antiseptic handwash drug product minus the active ingredient) and water. Consider using one of the same products used in the MUsT described above as the test consumer antiseptic handwash. Each subject is to follow the most recent or proposed directions of use for the test product, whenever the need to wash their hands occurs from randomization (Day 1) until Day 90 (Month 3).[11]

B. Alternatively, the comparator could be a nonantibacterial soap[12,13,14,15,16]; a justification for using such comparator as well as the composition of the formulation must be provided.

C. For an antibacterial indication, the recommended primary endpoint is the total number of episodes of skin infections in each arm of the study, as reported by each randomized subject from Day 1 until Day 90.

D. We encourage the submission of alternative proposals for trial designs that demonstrate a clinical benefit from the use of consumer antiseptic washes. A study in a properly selected enriched population, e.g., enrolling subjects at increased risk of developing an infection, might result in more infections overall and thus, require fewer subjects. If you opt to include subjects at increased risk of developing the primary endpoint, e.g., children or subjects with diabetes mellitus, weakened immunological status or chronic use of steroids, stratify the randomization, in order to assure that approximately equal numbers of each type of subject with an increased risk of developing the primary endpoint are enrolled in each arm of the study.[17]

E. We note that while a study of longer duration would likely accrue more infection events, it may also result in a significant number of subjects who prematurely discontinue from the study.

F. It is your responsibility to enroll sufficient subjects for the study to demonstrate a clinically and statistically significant difference between the treatment arms.

---

[11] The 3-month treatment duration recommendation is supported by a 2-period, crossover study (with each period being 10 weeks in duration) evaluating the use of a hand sanitizer containing benzalkonium chloride versus "normal" hand washing with soap and water, per Dyer DL et al. Alcohol-free instant hand sanitizer reduces elementary school illness absenteeism. *Fam Med.* 2000; 32 (633-8). The slightly longer 3-month treatment duration (rather than the 10-week treatment duration of this particular study) has been recommended for consumer antiseptic washes because consumer antiseptic hand rubs (commonly called hand sanitizers) could potentially have greater efficacy believed to be due to residual activity resulting in a persistent effect; however, many consumer antiseptic rubs are alcohol based.

[12] Larson EL et al. Effect of antibacterial home cleaning and handwashing products on infectious disease symptoms: a randomized double-blind trial. *Ann Intern Med.* 2004 Mar 2: 140 (5): 321.

[13] Luby SP et al. Effect of intensive handwashing promotion on childhood diarrhea in high-risk communities in Pakistan: a randomized controlled trial. *JAMA.* 2004 Jun 21; 291 (21): 2547-54.

[14] Luby SP et al. Effect of handwashing on child health: a randomized controlled trial. *Lancet.* 2005; 366: 275-33.

[15] Luby S et al. The effect of antibacterial soap on impetigo incidence, Karachi, Pakistan. *Am J Trop Med Hyg.* 2002 Oct; 67 (4): 430-5.

[16] Aiello AE et al. Consumer antibacterial soaps: effective or just risky? *Clin Infect Dis.* 2007 Sep 1; 45 (Suppl 2): S137-47.

[17] "One of the greatest difficulties in all studies concerning hygiene practices and infection is controlling for potential confounding variables. For example, if a study did not control for age and included adults as well as young children, the effect of a given hygiene intervention may be diluted since adults are at lower risk of diarrheal disease than children." per Aiello AE, Larson EL. What is the evidence for a causal link between hygiene and infections? *Lancet Infect Dis.* 2002 Feb; 2 (2): 103-10.

G. We recommend that the study be conducted in the United States or in a developed country with water and sanitation practices similar to those in the United States. If the study is conducted in an underdeveloped country with poor sanitation practices, such as open defecation, the results of the study are unlikely to be pertinent to the average American citizen who purchases and uses the test product.[18]

FDA is amenable to considering an antiviral claim for these products if the claim is adequately supported by efficacy data. An expanded indication would require both in vitro as well as in vivo supportive data. If you are seeking an antiviral indication or both an antiviral and an antibacterial indication, the recommended primary endpoint is the total number of episodes of skin infections[19] , acute respiratory illness, and diarrhea in each arm of the study, as reported by each randomized subject from Day 1 until Day 90. The overwhelming majority of upper respiratory tract infections are due to viruses. Viral diarrhea cases may also outnumber the bacterial diarrhea cases in the United States.

Next Steps

To move forward with the approach outlined in this letter, submit an acknowledgment of receipt of this letter to the docket within 60 days of the date of this letter and submit a statement of intent to conduct required studies to fill each data gap, as described above. Thereafter:

A. Submit an overall plan and timeline within 6 months of the date of this letter for completing each of the studies necessary to support a finding of safety and efficacy of benzethonium chloride for the indications discussed in the proposed rule. Ensure that your plan includes timelines for protocol submission, study initiation, study completion, and final study report submission for each required study.

B. Submit a report describing specific progress of all the ongoing studies by February 10, 2017.

C. Ensure that all study reports contain complete data sets, analysis, assessment, and interpretation.

Submit the acknowledgment letter, development plan, study protocols and reports and any other document or communication related to this matter to the docket (Docket No.FDA-1975-N-0012). Send a courtesy notification to the Division of Nonprescription Drug Products at the time of each submission.

In order to aid FDA's evaluation process, submit the items identified herein in a timely manner. We will reassess periodically whether continued deferral of final rulemaking is appropriate in light of the progress that has been made for each study.

---

[18] See e.g. Patil SR et al. The effect of India's total sanitation campaign on defecation behaviors and child health in rural Madya Pradesh: a cluster randomized controlled trial. *PLoS Med.* 2014 Aug 26; 11 (8): e1001709. doi: 10.1371/journal.pmed.1001709. eCollection 2014.

[19] Skin infections are more common in warm, humid environments, per Leonard RR. Prevention of superficial cutaneous infections. *Arch Dermatol.* 1967; 95 (5): 520-3 and Luby S et al. The effect of antibacterial soap on impetigo incidence, Karachi, Pakistan. *Am J Trop Med Hyg.* 2002 Oct; 67 (4): 430-5.

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

Sincerely,

Theresa M Michele, MD

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