PATTON BOGGS LLP
ATTORNEYS AT LAW

2550 M Street, NW
Washington, DC 20037-1350
202-457-6000

Facsimile 202-457-6315
www.pattonboggs.com

September 17, 2001

Daniel A. Kracov
202-457-5623
dkracov@pattonboggs.com

BY HAND

Charles Ganley, MD.
Director, Division of Over-the-Counter Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd., Room S-205
Rockville, MD 20850

Dear Dr. Ganley:

We are writing on behalf of Lonza Inc., to respectfully request that the Food and Drug Administration ("FDA") refrain from finalizing, in whole or in part, the topical antimicrobial drug products for over-&e-counter ("OTC") use monograph for health-care antiseptic drug products until all data on Benzethonium Chloride previously submitted, and to be submitted in the next Several months, is fully considered. These data include data, about which FDA has been informed, that are under development and will be submitted in the next several months.[1] These data clearly support the safety and efficacy of Benzethonium Chloride and should permit FDA to make a final determination to include Benzethonium Chloride as a permissible active ingredient in any partial or complete final health-care antiseptic drug products monograph.

Basis for Request

Set forth below is a review of the history of the topical antimicrobial products monograph, the consideration of Benzethonium Chloride in that monograph, the data submitted to FDA on Benzethonium Chloride, and industry's ongoing cooperation with FDA in providing all necessary data to support the safety and efficacy of the ingredient. This information supports our request that the topical antimicrobial products monograph

[1] We note that we are providing the additional efficacy data in response to FDA's only recently stated position that efficacy data was needed on the active ingredient.

75N-183H

C60

not be finalized, in whole or in part, without complete consideration of the status of Benzethonium Chloride as an active ingredient. A substantial amount of information supporting the safety and efficacy of Benzethonium Chloride has already been submitted to FDA. In addition, industry in general, and Lonza in particular, has diligently worked with FDA to develop the small amount of additional data that FDA has indicated is necessary to petit the agency to make a final determination regarding the classification of the ingredient as safe and effective in this monograph. Finalizing the monograph without fully considering all relevant data on Benzethonium Chloride, which Lonza believes would allow the inclusion of the ingredient in the monograph, would be unfair, detrimental to consumers, and inconsistent with FDA's actions with respect to other monographs.

A. Background on Topical Antimicrobial Products Monograph

As you know, in 1974 FDA published an advance notice of proposed r&making ("ANPR") to establish a monograph for OTC topical antimicrobial products, and invited comments.2 FDA scared that since many quaternary ammonium compounds ("quats") have detergent action which can aid in the removal of foreign material from a small wound, their use in the formulation of a skin wound cleanser is reasonable, and in the opinion of the Panel, safe. The concentration of quats was limited to 1/750 and FDA noted that an ingredient formulated in a skin wound cleanser would not need to possess antimicrobial activity. At the time, Benzethonium Chloride was classified in Category II for use in antimicrobial soap due to a physical and/or chemical incompatibility in formulation.

1. 1978 Tentative Final Monograph

In 1978, FDA published a notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products.3 In this tentative final monograph ("TFM") FDA acknowledged the "wide use and acceptance" of quats as antiseptics and disinfectants, and the particularly widespread use of such compounds for dipping solutions and "cold" instrument sterilization in hospitals.4 In the TFM, FDA classified the three quats for which data were submitted (benzalkonium chloride, Benzethonium

[2] 39 Fed. Reg. 33101 (Sept. 13, 1974).
[3] 43 Fed. Reg. 1210 (Jan. 6, 1978).
[4] Id.. at 1236.

Chloride, and methyl Benzethonium Chloride) in Category I for use in skin wound cleansers. FDA noted that toxic effects at use levels, for the three quats reviewed "would be unlikely" and that "there is little irritation potential with the use concentrations."[5]

FDA, however, concluded that there was insufficient evidence to allow the agency to come to a conclusion regarding the effectiveness of the quats since the effects of the quats *in vivo* on either resident cutaneous flora or on potentially pathogenic transients on the skin had nor been clearly demonstrated. FDA stated that *in vivo* effectiveness of quats for the product categories other than antimicrobial soap (and skin wound protectants) needed to be evaluated. FDA indicated that further safety data was only needed where appropriate for particular product classes, Although FDA found that reports showed that the application of quats to the skin reduced both the bacterial count on hands and in the axilla with subsequent reduction of body odor, the quats could nor be formulated into antimicrobial soap, and could not be categorized as generally recognized as safe or effective for such use.

FDA classified Benzethonium Chloride in Category III for use as a health-care personnel handwash, patient preoperative skin care preparation, skin antiseptic, skin wound protectant, and surgical hand scrub, concluding that adequate and well-controlled studies were not available at that time to permit the final classification of the active ingredients.

2. 1994 TFM

FDA published an amended TFM for OTC health-care antiseptic products in 1994, after considering public comments on the 1978 TFM and other information in the administrative record.6 Following the 1978 notice of proposed rulemaking, FDA had reopened the administrative record for the submission of new data in 1980, after the administrative record on the TFM had officially closed in 1978, FDA again reopened the administrative record for OTC topical antimicrobial drug products in January 5, 1982, to allow for consideration of the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products ("Miscellaneous External Panel") on mercury-containing drug products.[7] On May 21, 1982, FDA again reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of the

[5] Id., at 1237.
[6] 59 Fed. Reg. 31402 (June 17, 1994).
[7] 47 Fed. Reg. 436 (Jan. $1982).

recommendations of the Miscellaneous External Panel on alcohol drug products.[8] FDA issued a notice to reopen the administrative record for OTC topical antimicrobial drug products on Sept. 7, 1982, to consider the Miscellaneous External Panel's recommendations on topical antimicrobial drug products used for the treatment of diaper rash.[9] FDA also published a separate TFM for first aid uses of topical antimicrobials on July 22, 1991, in order to expedite the completion of the first aid section of the antimicrobial monograph.[10]

In the 1994 TFM, Benzethonium Chloride was classified as Class IIIE as a patient preoperative skin preparation, Class IIISE as an antiseptic handwash or health-care handwash, and class IIIE as a surgical hand scrub.[11] The 1994 TFM only briefly discusses the quats and the discussion focuses on comments submitted on Benzalkonium Chloride. Although FDA concluded that Benzalkonium Chloride remained Class III for use as a patient preoperative skin preparation, the 1994 TFM does include a discussion of Benzethonium Chloride. FDA noted that all of the quats remained in Category III at that time.[12]

B. Comments and Data Submitted to FDA on Benzethonium chloride

1. 1995 Lonza Submission

In response to the 1994 TFM, Lonza submitted several toxicology studies in support of a Category I safety classification for Benzethonium Chloride as a health-care antiseptic handwash on December 14, 1995. The studies included two lifetime dermal studies, a developmental toxicity study, and several articles from the published literature. In addition, Lonza convened an expert panel of toxicologists to evaluate the safety data on Benzethonium Chloride. The expert panel's report was also included in Lonza's December 14, 1995, submission.13 In a December 22, 1995, letter, Lonza requested a

[8] 47 Fed. Reg. 22324 (May 21, 1982).
[9] 47 Fed. Reg. 39406 (Sept. 7, 1982).
[10] 56 Fed. Reg. 33644 (July 22, 1991).
[11] 59 Fed. Reg. 3 1402,
[12] 59 Fed. Reg. 31402, 31426 (June 17, 1994).
[13] The expert panel concluded that the database was adequate to evaluate the safety of using Benzethonium Chloride as an antimicrobial agent in consumer hmd soap products and that this database supports the opinion that this use pattern will not be associated with any unacceptable risks. Expert Panel Review of Benzethonium Chloride, volume I: "Panel Commentary."

meeting with FDA scientists to discuss the expert panel report and the supporting data. Lonza's stated objective for seeking that meeting was to obtain FDA feedback on whether the data submitted on December 14, 1995, adequately supported a Category I safety classification for Benzethonium Chloride as a health-care antiseptic handwash.

2. 1998 Meeting with FDA and Subsequent Submissions

FDA's response to Lonza's 1995 submission of safety data on Benzethonium Chloride came in a brief April 1, 1998, meeting with members of FDA's Center for Drug Evaluation and Research, Office of Drug Evaluation., Division of OTC Products ("DOTCP"). The DOTCP scientists indicated that they found the data submitted by Lonza in 1995 to be adequate to assess the safety of Benzethonium Chloride for use as an antimicrobial agent in health-care antiseptic handsoaps. The only concern raised by the data was the delivery solvent used in one toxicity study, and DOTCP requested another toxicity study, encouraging Lonza to conduct and submit this study as soon as possible Lonza understood that these data would allow FDA to conclude that Benzethonium Chloride could be classified in the monograph as Category I for safety.

a. Proposed Alternative Studies

Lonza and FDA continued to discuss the studies necessary to support a determination regarding the status of Benzethonium Chloride for several months in 1998. Lonza reiterated its commitment to conducting the additional toxicology work needed to address FDA's concerns regarding the safety of the ingredient. Lonza also proposed alternative studies that were more feasible to conduct and would provide FDA with more useful data

In an August 12, 1998, letter, Lonza provided additional information regarding the proposed alternate studies, and Lonza and FDA held a teleconference on August 26, 1998, to discuss alternate toxicity studies. During that teleconference, FDA agreed to alternative studies that could be submitted to support the safety of Benzethonium Chloride, including dermal penetration and dermal, toxicokinetic studies. FDA urged Lonza to submit protocols for both studies before proceeding with any testing. Lonza submitted an outline for the proposed pharmacokinetic study in a December 7, 1998, letter, and noted that the dermal penetration studies would be standard studies for which definitive protocols would be developed and submitted for FDA review once agreement

was reached on the design for the pharmacokinetic study. Based on its interaction with the agency, Lonza believed that once these data were submitted, FDA would be able to make a determination regarding the safety of Benzethonium Chloride under the monograph.

3. Additional Studies Submitted by Lonza

On October 10, 2000, Lonza submitted the dermal absorption and pharmacokinetic studies that had been requested by FDA in 1998 to support Category I status for Benzethonium Chloride as a health-care antiseptic drug product. This submission included an overview of Benzethonium Chloride studies, a dermal absorption study, a pharmacokinetics study, and a dermal irritation study. Also included in this October 10, 2000, submission were efficacy studies in support of Category I status for Benzethonium Chloride, including a Minimum Inhibitory Concentration ("MIC") study. Lonza has been actively pursuing a meeting with the appropriate Agency personnel -- without success -- to determine the review status of the submitted studies and whether any additional data was required to demonstrate the safety of the Benzethonium Chloride.

C. Benzethonium Chloride Should be Included in any Finalized Monograph

1. Adequate Data Submitted to Demonstrate Safety

A significant amount of data has been submitted to FDA on the use of Benzethonium Chloride as an active ingredient in health-care antiseptic drug products. The agency has had ample time to consider these data, which provide adequate support for the ingredient's safety when used in health-care antiseptic drug products. These additional data represent a relatively small amount of information that the Agency should have no trouble reviewing in a short period of time, to allow for the inclusion of benzethonium chloride in any partial or complete final monograph relating to this class of drug products. The recently submitted data further support the conclusion that Benzethonium Chloride is safe for use in health-care antiseptic drug products. Lonza has actively pursued the support of Benzethonium Chloride by requesting meetings, addressing data requirements and generating agreed-upon safety studies.

2. Adequate Data Submitted to Demonstrate Efficacy

A significant amount of data has also been submitted to FDA to support the efficacy of Benzethonium Chloride as an active ingredient in health-care antiseptic drug products, and Lonza will shortly be submitting additional efficacy data on product formulations, incorporating Benzethonium Chloride. Specifically, when FDA initially indicated that efficacy data was only required on the active ingredient in health-care antiseptic drug products to support Category I classification for efficacy, Lonza submitted such data, including MIC studies. Lonza understood that end users of rhe ingredient would be responsible for showing that the finished formulation complied with the monograph. FDA later indicated that efficacy data was required on finished formulations to support a determination regarding the efficacy of the active ingredient. Consequently, Lonza has undertaken efficacy studies on finished formulations containing Benzethonium Chloride that will be completed in the next several months and submitted to FDA immediately thereafter.

Lonza notes that while the data required for finished formulations containing Benzethonium Chloride is well beyond that which FDA normally requires for OTC drug products, Lonza is committed to providing the agency all data necessary to permit a final conclusion regarding the efficacy of the ingredient. The data on efficacy that have already been submitted to FDA on the active ingredient, as well as the data that will be submitted to FDA shortly on finished formulations, should be more than adequate to support the efficacy of Benzethonium Chloride for use in he&h-care antiseptics.

3. Additional Data on Benzethonium Chloride Should be Considered Prior to Finalization of Monograph

As *noted* above, additional data are being developed to address FDA's expressed concerns regarding the efficacy of the ingredient. The ongoing communication between FDA and industry regarding the monograph status of the ingredient indicates industry's strong commitment to provide all data necessary to support Category I status for the ingredient in any partial or complete final health-care antiseptic monograph. In the twenty years since a monograph on health-care antiseptic drug products was first proposed, FDA has previously reopened the record to the monograph a number of rimes to permit the consideration of other ingredients, without concern that doing so would unduly delay the finalization of the monograph. In addition, industry has made

PATTON BOGGS LLP
ATTORNEYS AT LAW

considerable efforts to provide FDA the needed data to support the inclusion of Benzethonium Chloride in the final monograph. FDA has indicated that only a small amount of additional data would be needed to allow the agency to make a final determination regarding the safety and efficacy of Benzethonium Chloride. Given the long history of the monograph, the numerous reopenings of the record to the monograph for consideration of other ingredients, and the ongoing dialogue with industry regarding Benzethonium Chloride, we ask FDA to consider the interests of consumers and industry, act in a fair manner, and refrain from finalizing the health-care antiseptic monograph in whole or part, without allowing for the review and consideration of this data and any additional information that FDA determines is needed to conclude that Benzethonium Chloride is safe and effective for use as a health-care antiseptic ingredient.

Conclusion

Lonza respectfully requests that the Agency refrain from finalizing the monograph for heal&-care antiseptic OTC drug products in whole or part, until all data on Benzethonium Chloride as an active ingredient are fully reviewed and considered. These data should support fully the safety and efficacy of Benzethonium Chloride and permit FDA to make a final determination to include Benzethonium Chloride as a permissible ingredient in the final monograph. Any resulting delay would be minimal, particularly considering the long history of the monograph review for this class of drug products. Excluding Benzethonium Chloride from the final monograph would be unfair to consumers and industry.

We appreciate your time and attention to this matter, and look forward to y-our response to our request.

Sincerely,

Daniel A. Kracov

Counsel to Lonza, Inc.