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January 12, 2004

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Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Topical Antimicrobial Drug Products for Over-the-Counter Human Use:
Health-Care Antiseptic Drug Products [Docket No. 75N-183H]

Dear Sir or Madam:

On October 21, 2002, Lonza, Inc. submitted additional data on benzethonium chloride ("BZC") further supporting the finding that BZC is Category I¹ under the above-referenced monograph. We understand that the data are still under review, and look forward to meeting with you when your review is sufficiently advanced. Until that time, we note the following:²

- (1) Lonza, Inc. has had a highly conservative risk assessment prepared by its toxicology consultant, Dr. Gerald Schoenig, for BZC for the non-alcohol hand sanitizer ("NAHS") use pattern. This risk assessment shows a potential safety factor of 312 for this use pattern, and it is consistent with the Cosmetics Ingredient Review ("CIR") for BZC, which concluded that BZC is safe at

¹ (1) November 30, 2000, Final Report, "Determination of the Antimicrobial Efficacy of One Test Product and one Reference Product Using Health Care Personnel Handwash Procedure); (2) November 30, 2000, Final Report, "Evaluation of One Test Product for Its Antimicrobial Properties When Challenged from Various Microorganism Strains Using an In-Vitro Time-Kill Method;" and (3) November 30, 2000, Final Report, "Determination of the Minimum Inhibitory Concentration (MIC) of One Product When Challenged with Various Microorganism Strains Using the Macrodilution Broth Method."

² It has recently come to our attention that GOJO Industries, Inc. ("GOJO") submitted a letter to the docket alleging that there is insufficient data to assure the safety and efficacy of BZC for use in leave-on (no rinse) products. GOJO's "concerns" have never been proven and/or fail to take into account the recent safety and efficacy data that have been submitted to this docket. It is unfortunate that GOJO would attempt to use the regulatory process for anti-competitive purposes. See Letter from GOJO Industries, Inc. to the Food and Drug Administration ("FDA"), Docket No. 75N-183H, dated August 27, 2003.

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concentrations of up to 0.5% in both rinse off and leave on cosmetic products.³
The risk assessment is attached.

- (2) Although A.D. Russell has observed that staphylococcal strains resistant to antibiotics have the potential to be resistant to cationic biocides (*e.g.*, BZC), Russell also conceded that “the clinical relevance of this possibility remains contentious.” Moreover, Russell’s statement was in the context of a broader discussion of chlorhexidine, not BZC.⁴
- (3) Recent papers indicating that bacteria resistant to quaternary ammonium compounds are not generally antibiotic resistant include:
 - (a) J.A. Joyson, *et al.*, *Adaptive resistance to benzalkonium chloride, amikacin, and tobramycin: the effect on susceptibility to other antimicrobials*, 93 *J. Appl. Microbiol.* 96 (2002).
 - (b) A.J. McBain, *et al.*, *Possible implications of biocide accumulation in the environment on the prevalence of bacterial antibiotic resistance*, 29 *J. Indust. Microbiol. Biotech.* 326 (2002).
 - (c) P. Gilbert and A.J. McBain, *Potential Impact of Increased Use of Biocides in Consumer Products on the Prevalence of Antibiotic Resistance*, 16 *Clin. Microbiol. Rev.* 189 (2003).
 - (d) M.F. Loughlin, *et al.*, *Pseudomonas aeruginosa cells adapted to benzalkonium chloride show resistance to other membrane-active agents but not to clinically relevant antibiotics*, 49 *Antimicrobial Chemotherapy* 631 (2002).

³ Schoenig Risk Assessment, Attachment 1.

⁴ A.D. Russell, *Possible Link Between Bacterial Resistance and Use of Antibiotics and Biocides*, 42 *Antimicrobial Agents and Chemotherapy* 2151 (Aug. 1998).



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We look forward to meeting with you in the near future. In the interim, please do not hesitate to contact us if you have comments or questions concerning BZC.

Respectfully submitted,

A handwritten signature in cursive script that reads 'Daniel A. Kracov'.

Daniel A. Kracov

Counsel to Lonza, Inc.



TOXICOLOGY/REGULATORY SERVICES, INC.

**Quantitative Risk Assessment for the Use of Benzethonium Chloride (BZC)
as the Active Ingredient in Non-Alcoholic Hand Sanitizer Products
for Health Care Workers**

Prepared by:
Gerald P. Schoenig, PhD.
December 23, 2003

Assumptions:

Quantity of product used per wash	1.5 g ^a
Number of washes per day	24 ^b
Maximum percentage of BZC in leave-on hand sanitizer products	0.2%
Percent dermal absorption of BZC through human skin	4.71% ^c
Average body weight of female health care worker	60 kg
NOAEL from animal toxicology studies	12.5 mg/kg/day ^d

^a Personal communications with Dial Corporation.

^b Voss, A. and Widmer, A. F. (1997). No Time for Handwashing! Handwashing Versus Alcoholic Rub: Can We Afford 100% Compliance? *Infection Control and Hospital Epidemiology* 18:205-208.

^c Unpublished study entitled "The *In vitro* Percutaneous Absorption of ¹⁴C-Benzethonium Chloride Through Rat Skin at an Incorporation Rate of 0.1% (w/v) in GMS Cream and Ethanol," Inveresk Research. October 15, 2002.

^d There are three studies that provide information regarding the No Observed Adverse Effect Level (NOAEL) for BZC. One of these studies is a rat 28-day oral toxicity study, the second is a rat developmental toxicity study and the third is a rat two-year chronic oral toxicity study. The NOAELs in these studies are 40, 100 and 125 mg/kg/day, respectively. No developmental effects were observed in the developmental toxicity study and the NOAEL is based upon maternal toxicity. The former two studies are recent guideline studies while the latter study was conducted in the 1950s. Therefore, a 10-fold uncertainty factor was applied to the latter study resulting in a NOAEL of 12.5 mg/kg/day. This lower NOAEL was used in this risk assessment.

Safety Factor Calculations:

1.5 g product/wash x 24 washes/day x $\frac{5}{7}$ days/week		25.7 g product/day
25.7 g product x 0.002 =		0.05 g BZC/day
0.05 g BZC/day x 0.0471 =		0.0024 g BZC absorbed/day
0.0024 g BZC/day x 1000 =		2.40 mg BZC absorbed/day
$\frac{2.40 \text{ mg BZC absorbed/day}}{60 \text{ kg}}$	=	0.04 mg BZC absorbed/kg/day

$$\text{Safety Factor} = \frac{\text{NOAEL for Systemic Toxicity}}{\text{Systemic Exposure}} = \frac{12.5 \text{ mg/kg/day}}{0.04 \text{ mg/kg/day}} = 312$$

Conservatism Included in Risk Assessment:

1. Only the maximum incorporation rate was considered.
2. The assumption that a health care worker would use a leave-on hand sanitizer product 24 times per day assumes high end of current compliance, i.e. 3 hand washes per hour.
3. Under the controlled conditions specified by the protocol for the *in vitro* skin penetration study, the results would be expected to exaggerate the amount of dermal absorption that would occur under normal human use conditions. This is particularly true in this case since the amount of radiolabeled BZC found in the epidermis was included in the absorbed material. The reason for this is that only a minimum number of tape strips were used to remove the stratum cornea in this study.
4. The lowest applicable NOAEL was used to define the NOAEL used in this risk assessment.
5. No consideration was given to the fact that a large portion of the BZC that would come in contact with the skin would be washed off during hand washing with soap and water or during baths or showers.