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May 15, 2002

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Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Resources  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20857

**Re: Citizen Petition; Docket No. 75N-183H; Topical Antimicrobial Drug Products for OTC Use; Tentative Final Monograph for First Aid Antiseptic Drug Products**

Dear Sir/Madam:

On behalf of our client, Lonza Inc., we are submitting this Citizen Petition under 21 C.F.R. § 10.30, to respectfully request that the Food and Drug Administration ("FDA") re-open the administrative record to allow for the submission and evaluation of additional data supporting the Category I safety and efficacy classification of benzethonium chloride ("BZC") in the topical antimicrobial drug products for over-the-counter ("OTC") use monograph for health-care antiseptic drug products and any planned final monographs for consumer use antiseptic drug products. We understand from our previous correspondence and discussions with FDA that the Agency intends to consider all data that have been submitted on BZC prior to further action on the health-care antiseptic drug products monograph, and we are submitting this Citizen Petition to ensure that our formal request for the consideration of these additional data is included in the administrative record. The additional data being submitted with this petition include efficacy and skin and eye irritation studies.

In addition to the efficacy and skin and eye irritation data, Lonza also is resubmitting, for the convenience of FDA reviewers, other pertinent safety and efficacy data. These data include a dermal absorption study, a pharmacokinetics study, a dermal irritation study and an efficacy study that were originally submitted in October 2000. All of the studies and documents included with this petition are listed in Attachment 1.

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The data on BZC submitted to FDA to date, which includes long-term bioassays in two species, developmental toxicity and mutagenicity studies, and with this Citizen Petition clearly support BZC's safety and efficacy and should permit FDA to make a final determination to include BZC as a permissible active ingredient in any partial or complete health-care antiseptic drug products final monograph. In addition, industry in general, and Lonza in particular, has diligently worked with FDA to develop the additional data that FDA indicated was necessary to permit the agency to make a final determination regarding the classification of BZC as safe and effective in this monograph.

A detailed discussion of the additional efficacy and skin and eye irritation data is set forth below.

#### **Discussion of Additional Efficacy Data**

Like many other quaternary ammonium compounds, BZC demonstrates significant antimicrobial activity. This activity primarily comes from a multi-site attack on the cell membranes of both Gram-positive and Gram-negative bacteria as well as yeast and fungi. Membrane enveloped viruses are similarly targeted. Data on the efficacy of BZC has been developed using the *in-vitro* Minimum Inhibitory Concentration (MIC) test and Time Kill-studies and a clinical study using the Health Care Personnel Handwash assay. The MIC study was originally submitted to FDA on October 20, 2000 and the Time-Kill and Health-Care Personnel Handwash studies are included with this Citizen Petition. The testing methods used in the studies are based on the methods referenced in the Tentative Final Monograph (TFM) for Topical Antimicrobial Drug Products. The studies clearly show that BZC, either by itself or in a formulated antibacterial hand soap (ABHS), is an effective antimicrobial ingredient and meets the requirements for classification as Category IE for Health-Care Antiseptic Handwashes and Antiseptic Handwashes.

Summaries of the studies being submitted with this petition (MIC, Time-Kill and Health-Care Personnel Handwash studies) are presented below.

- **In vitro Assays (MIC and Time-Kill)**

In the MIC assay (Volume 1), BZC was evaluated against fifty (50) microorganisms. BZC showed complete inhibition of bacterial growth at 24 hours exposure, with concentrations ranging from a low of  $\leq 0.76$  parts-per-million (ppm) up to 98 ppm. The microorganisms tested were those listed in the TFM section on MIC testing.

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The Time-Kill assay (Volume 2) tested the antimicrobial efficacy of a formulated ABHS containing 0.5% BZC. A 50% dilution of this product (0.25% BZC) was challenged with test bacteria and after thirty (30 seconds) or one (1) minute exposure the surviving bacteria were enumerated. Log<sub>10</sub> reduction was based on comparison to the number of bacteria in the control preparations. Preliminary Till-Kill assays vs. a representative series of bacteria demonstrated that the ABHS Base without BZC did not have antibacterial activity. Greater than 2 log<sub>10</sub> or 3 log<sub>10</sub> reductions in the number of bacteria were noted at both 30 seconds and one minute sampling times, even though the bacteria were actually exposed to only 0.25% BZC. The dilution rate of 50% is based on recommendations made by the Soap and Detergent Association and Cosmetic, Toiletry, and Fragrance Association Industry Coalition, Proposals for Finished Product Efficacy Testing of Health Care Antiseptic Drug Products). The pathogenic species and antibiotic-resistant bacteria as well as the commensal microbes were significantly reduced by exposure to the ABHS containing BZC.

- In Vivo Assays

The protocol used for the Health-Care Personnel Handwash Assay (Volume 3) was based on ASTM Method E1174-00. The assay used a large panel (75) of informed volunteers to evaluate the potential of hand washing formulations to reduce transient microbial flora. The assay used the marker organism *Serratia marcescens*. ABHS formulations used with and without BZC were tested. In addition, both hands of each volunteer were examined before and after testing and scored for skin irritation including redness, cracks or fissures, scaling and roughness. The test results are presented on Table 1 below. In brief, the ABHS formulation containing 0.5% BZC achieved a 1.87 log<sub>10</sub> reduction after the first wash and a reduction of 2.61 log<sub>10</sub> after eleven (11) repetitive washes. The ABHS formulation without BZC (ABHS base) achieved a 1.82 log<sub>10</sub> after the first wash and a 2.1 log<sub>10</sub> reduction after the eleventh wash. The ABHS containing 0.5% BZC was significantly better in reducing the level of marker organism than the ABHS base. Examination of the volunteers hands after the last washing with the ABHS containing 0.5% BZC did not show any skin irritation. These results demonstrate that the presence of 0.5% BZC in this ABHS formulation is responsible for the significantly improved antibacterial efficacy over the ABHS base formulation.

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**Table 1**  
**Log<sub>10</sub> and Percent Reduction of Bacteria in the Health Care**  
**Personnel Handwash Assay**

Treatment	Log <sub>10</sub> Reduction after first wash	Log <sub>10</sub> Reduction after 11 <sup>th</sup> wash	Percent Reduction after first wash	Percent Reduction after 11 <sup>th</sup> wash
ABHS with 0.5% BZC	1.87	2.61	98.64%	99.75%
ABHS base – without BZC	1.82	2.1	98.50%	99.12%

**Discussion of Eye and Skin Irritation Data**

Included in this submission are data that have been developed to evaluate the eye and skin irritation potential of BZC when it is incorporated into prototype antibacterial hand soap formulations.

- **Eye Irritation Studies**

Eye irritation potential was evaluated by conducting standard Draize eye irritation tests with three different concentrations of BZC (1.0, 1.5 and 2.0%) in a prototype antibacterial hand soap formulation. Also included in this series of tests were two representative commercially available antibacterial hand soap formulations. The results of these tests are summarized in Table 2 below. The findings from this series of tests showed that the degree of irritation observed with the prototype formulation containing 1.0% BZC was similar to that produced by the two commercially available antibacterial hand soap formulations. At a 1.5% BZC incorporation rate, the degree of irritation was slightly more than that observed with the two commercially available antibacterial hand soap formulations that were included in this series of tests, but still within the acceptable range since all irritation cleared within seven days. An unacceptable level of irritation was observed at a 2.0% BZC incorporation rate since irritation did not clear within seven days. While an unacceptable level of irritation was observed at a 2.0% BZC incorporation rate with this particular prototype formulation, it is likely that BZC at this or even higher levels could be incorporated in other ABHS formulations without

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incurring an unacceptable level of eye irritation. Copies of the laboratory reports for the eye irritation studies can be found in Volume 4 of this submission.

**Table 2**  
**Summary of Primary Eye Irritation Test Results with Lonza, Inc.'s Prototype**  
**Antibacterial Hand Soap Formulation**

Substance	1 hour				24 hours				48 hours				72 hours			
	Cornea	Iris	Conj	Total	Cornea	Iris	Conj	Total	Cornea	Iris	Conj	Total	Cornea	Iris	Conj	Total
Representative Commercial Hand Soap #1	0.0	0.0	14.0	14.0	5.0	1.7	12.0	18.7	5.0	0.0	6.7	11.7	1.7	0.0	2.7	4.3
Representative Commercial Hand Soap #2	0.0	0.0	11.3	11.3	5.0	0.0	9.3	14.3	5.0	0.0	5.3	10.3	5.0	0.0	2.7	7.7
Lonza Formulation PC-ABHS 1.0 NT	0.0	0.0	9.3	9.3	3.3	1.7	8.7	13.7	1.7	0.0	4.7	6.3	1.7	0.0	3.3	5.0
Lonza Formulation PC-ABHS 1.5 NT	0.0	0.0	11.3	11.3	8.3	0.0	10.0	18.3	5.0	1.7	10.0	16.7	5.0	1.7	10.7	17.3
Lonza Formulation PC-ABHS 2.0 NT	1.7	1.7	12.6	16.0	11.7	1.7	10.7	24.0	10.0	1.7	10.0	21.7	8.3	1.7	10.0	20.0

Note: Three animals were used for each test.

**Table 2 (continued)**

Substance	Day 4				Day 7				Day 10			
	Cornea	Iris	Conj	Total	Cornea	Iris	Conj	Total	Cornea	Iris	Conj	Total
Representative Commercial Hand Soap #1	0.0	0.0	0.0	0.0	--	--	--	--	--	--	--	--
Representative Commercial Hand Soap #2	0.0	0.0	0.0	0.0	--	--	--	--	--	--	--	--
Lonza Formulation PC-ABHS 1.0 NT	0.0	0.0	1.3	1.3	0.0	0.0	0.0	0.0	--	--	--	--
Lonza Formulation PC-ABHS 1.5 NT	1.7	0.0	4.7	6.3	0.0	0.0	0.0	0.0	--	--	--	--
Lonza Formulation PC-ABHS 2.0 NT	5.0	1.7	6.0	12.7	3.3	0.0	2.0	5.3	3.3(2)	0.0	2.0	5.3

Note: Numbers in parentheses ( ) indicate number of rabbits with corneal opacity when n is less than 3.

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- Skin Irritation Studies

Two types of studies were conducted to evaluate the skin irritation potential of BZC in prototype antibacterial hand soap formulations. Lonza, Inc. conducted standard Draize skin irritation tests with its prototype formulation and another company interested in using BZC in its line of antibacterial hand soap formulations conducted Human Repeat Application Soap Chamber Cumulative Irritation Tests in human volunteers using its prototype formulation.

Included in Lonza Inc.'s test series were the same two representative commercially available antibacterial hand soap formulations used in the eye irritation tests and its prototype formulation fortified with 2.0% BZC. Similar findings were obtained with all three formulations indicating that BZC incorporation of 2.0% did not produce an unacceptable level of skin irritation. These data are summarized in Table 3 below. Copies of the laboratory reports for the skin irritation studies can be found in Volume 5 of this submission.

**Table 3**  
**Summary of Primary Skin Irritation Test Results with Lonza, Inc.'s Prototype Antibacterial Hand Soap Formulation**

Substance		1 hour	24 hours	48 hours	72 hours	Day 7
<b>Representative Commercial Hand Soap #1</b>	Erythema	2.0	2.0	1.3	1.3	0.0
	Edema	1.0	0.3	0.0	0.0	0.0
<b>Representative Commercial Hand Soap #2</b>	Erythema	2.0	1.3	0.7	0.7	0.0
	Edema	1.0	0.0	0.0	0.0	0.0
<b>Lonza Formulation PC-ABHS 2.0 NT</b>	Erythema	1.3	1.7	1.7	1.3	0.0
	Edema	0.0	0.0	0.7	0.3	0.0

The results of the Human Repeat Application Soap Chamber Cumulative Irritation Tests are described in an Executive Summary entitled "Clinical Evaluation of the Skin Irritation Profile of Commercially-Available Antibacterial Hand Soaps Using Repeat Application Soap Chamber Cumulative Irritation Tests." Copies of Executive Summary and the laboratory reports supporting the discussion in the Executive Summary can be found in Volume 6 of this submission (For confidentiality reasons, the sponsor identity has been removed from the reports). The findings from this series of tests showed that the prototype antibacterial hand

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soap formulation containing BZC as an active ingredient at incorporation rates of 0.5% and 2.0% has less or equivalent potential for skin irritation following repeated exposure than the commercially available antibacterial hand soaps that were included in the tests as benchmark comparators.

**Data Previously Submitted**

As noted above, for the convenience of FDA reviewers, Lonza is resubmitting a dermal absorption study, a pharmacokinetics study, and a dermal irritation study originally submitted in October 2000 (Volume 7). The efficacy study also submitted in October 2000 can be found in Volume 1.

**Summary and Conclusions**

The overall conclusion of these series of eye and skin irritation tests is that eye and skin irritation will not limit the use of BZC as an active ingredient in antibacterial hand soap formulations at concentrations needed for efficacy

Moreover, as noted above, the additional data contained herein support Category IE and IS status for BZC in the final monograph for health care antiseptic drug products and any planned final monographs for consumer use antiseptic drug products.

Thank you for your consideration of our request that the administrative record be re-opened to permit the review of all data relevant to the safety and efficacy evaluation of BZC in the topical antimicrobial drug products for OTC use monograph for health-care antiseptic drug products.

**Environmental Impact**

Pursuant to FDA regulations, action on an OTC monograph that does not increase the use of the active moiety, or if it increases the use of the active moiety the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion, is categorically excluded from an environmental impact assessment. 21 C.F.R. § 25.31(a)-(b). Thus, no environmental assessment is required.

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**Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition contains all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

A handwritten signature in black ink, appearing to read 'D. Kracov', with a long horizontal flourish extending to the right.

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**ATTACHMENT 1**  
**List of Studies Included with This Petition**

Title Volume Number Tab Number

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**EFFICACY STUDIES**

Determination of the Minimum Inhibitory Concentration (MIC) of One Product When Challenged With Fifty Microorganism Strains Using the Macro-Dilution Broth Method	1	--
Assessment of Rapid Germicidal (Time Kill) Activity for Antibacterial Hand Soaps	2	--
Efficacy Evaluation of Health-Care Personnel Handwash Products	3	--

**EYE IRRITATION STUDIES**

Primary Eye Irritation Test with Representative Commercial Antibacterial Liquid Hand Soap #1	4	A
Primary Eye Irritation Test with Representative Commercial Antibacterial Liquid Hand Soap #2	4	B
Primary Eye Irritation Test with Lonza Formulation PC-ABHS-1.0 NT	4	C
Primary Eye Irritation Test with Lonza Formulation PC-ABHS-1.5 NT	4	D
Primary Eye Irritation Test with Lonza Formulation PC-ABHS-2.0 NT	4	E

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**ATTACHMENT 1 (continued)**  
**List of Studies Included with This Petition**

Title Volume Number Tab Number

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**SKIN IRRITATION STUDIES**

Primary Skin Irritation Test in Rabbits with Representative Commercial Antibacterial Liquid Hand Soap #1	5	A
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Primary Skin Irritation Test in Rabbits with Representative Commercial Antibacterial Liquid Hand Soap #2	5	B
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Primary Skin Irritation Test with Lonza Formulation PC-ABHS-2.0 NT	5	C
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Clinical Evaluation of the Skin Irritation Profile Of Commercially-Available Antibacterial Hand Soaps Using Repeat Application Soap Chamber Cumulative Irritation Tests	6	--
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**DERMAL ABSORPTION, PHARMACOKINETICS AND IRRITATION STUDIES**

The In-Vitro Percutaneous Absorption of [ <sup>14</sup> C]-Benzethonium Chloride Through Human and Rat Skin	7	A
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Dermal Irritation of Benzethonium Chloride in Rats	7	B
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Preliminary Pharmacokinetics Study of Dermally Applied <sup>14</sup> C-Benzethonium Chloride in Rats	7	C
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