WOODWARD LABORATORIES

October 28, 2003

Dockets Management Branch

Food and Drug Administration (HFA-305)

5630 Fishers Lane, Room 1061

Rockville, MD 20852

Re: Proposed Rule; Reopening of the Administrative Record for Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health-Care Antiseptic Drug Products. 68 Fed. Reg. 32003. (May 29, 2003). [Docket No. 75N-183H]

Dear Sir/Madam

Woodward Laboratories, Inc. is submitting these comments in response to the Food and Drug Administration's reopening of the administrative record for the tentative final monograph for Over-the-Counter Health-Care antiseptic Drug products, 59 Fed. Reg. 31402 (June 17, 1994). **These comments are submitted in support of the safety and efficacy of benzalkonium chloride as active antimicrobial agent in leave-on products.**

Summary: Benzalkonium chloride is a quaternary ammonium compound that has a widespread utility in the health care industry as broad-spectrum antimicrobial active

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agents, and in the cosmetic industry as foaming and cleansing agents, conditioners and bactericides.

The Food and Drug Administration has previously determined that benzalkonium chloride (0.1% - 0.13% w/w) is generally recognized as safe and effective as an active for antiseptic drug products[1]. Benzalkonium chloride has also been recognized as a safe and effective active ingredient for oral rinse/mouthwash products[2]. Furthermore, benzalkonium chloride as an active in rinse-free hand sanitizer applications meets the performance criteria designated under the Tentative Final Monograph for Healthcare Antiseptic Drug Products[3-5]. Two studies of the effectiveness of a benzalkonium chloride-containing instant hand sanitizer at reducing illness absenteeism in elementary schools support the application's safety and effectiveness[6,7]. Finally, an expert panel that was convened to review data concerning the safety of benzalkonium chloride determined that at concentrations up to 0.1% free active ingredient is safe for human use[8].

We assert that:

1. Sufficient evidence exists to support the use of benzalkonium chloride as a Category 1 active ingredient in leave-on (non-rinse) sanitizer category described in the 1994 tentative final monograph for healthcare personnel antiseptic drug products.
2. The safety and antimicrobial effectiveness profiles, and general utility of benzalkonium chloride in private and industrial applications indicates that the active ingredient is suitable for leave-on products, and that limiting the use of this active ingredient to only those products that are rinsed off of the skin is not warranted.

3. The potential for development of bacterial resistance in a wide variety of topical sanitizer applications has been widely addressed in the literature. No evidence exists to suggest that leave-on antiseptic applications produce bacterial resistance in non-laboratory settings.

Background:

The FDA has acknowledged the usefulness of biocidal quaternary amine actives, in particular benzalkonium chloride, in previous rulemaking. For example, in the 1991 Proposed Rule for Topical Antiseptic Drug Products for Over-The –Counter Human Use; Tentative Final Monograph for First Aid Antiseptic Drug Products, FDA restated that "it was not seriously concerned with the safety of "quats" for 'first-aid' uses, i.e. skin wound cleansers, skin wound protectants, and skin antiseptics"[1]. Based on the data submitted to the expert review panel at that time, benzalkonium chloride was found to meet monograph conditions for first-aid antiseptic applications. Other quaternary amine actives found to meet the tentative final monograph conditions included benzethonium chloride, and methyl benzethonium chloride, all intended for acute (≤7 days) application. In addition, FDA has allowed a combination of benzalkonium chloride and benzethonium chloride homologues at concentrations of up to 0.004% for food preservative (long-term ingestible) applications[9].

Safety:

The Sixteenth Report of the Cosmetic Ingredients Review Expert Panel[8] and the 2002 Cosmetic Ingredient Review[10] considers benzalkonium chloride to be safe at concentrations of up to 0.1% w/w. Such cosmetic applications are clearly intended to

encompass a daily-use regimen. In addition, a 10-week, open label, crossover study involving 420 elementary school-age children (ages 5-12) was published[6]. In the course of the study, students were instructed to use the leave-on sanitizer 1) immediately upon entering the classroom, 2) before eating (snacks and lunch), 3) after sneezing or coughing in the classroom, and 4) after using the restroom. Each application delivered approximately 0.25 ml via a spritz dispenser, and compliance was monitored by weighing bottles periodically during the study. Even with this monitored, frequent use schedule, no adverse events (edema, rash, erythema) were reported either during or after the study's completion.

The safety of leave-on sanitizers containing benzalkonium chloride is further supported by direct market experience. One product, manufactured by Woodward Laboratories, Inc. (HandClens Instant Hand Sanitizer) has been marketed since 1998, with a total sales volume of approximately one hundred thousand units, and with no adverse events reported[11].

In terms of application safety, it must be also pointed out that many leave-on sanitizer applications that contain benzalkonium chloride are alcohol-free, and therefore non-flammable. This presents a distinct utility in settings where the use of a flammable leave-on sanitizer, such as alcohol-based leave-on sanitizers, is not safe or appropriate. Such settings include airlines, hospital rooms with oxygen-feeds, schools and prisons (these last two are also examples wherein the potential for ingestion renders alcohol products uacceptable).

Effectiveness

In 1994, FDA issued a set of performance guidelines to assist industry in the development of health care personnel hand washes[3]. Because there is an increased advocacy for the use of leave-on sanitizer applications in health care settings, we strongly believe that the existing FDA protocol should be maintained as an accurate and meaningful test of performance of leave-on sanitizer applications, in that it requires products to display a significant and relatively uniform persistence and continued antimicrobial action under a heavy soil load. Several publications support the effectiveness of leave-on products containing benzalkonium chloride under the given performance standards. For example, a study published in 1998 examined the performance of a benzalkonium chloride-containing, alcohol-free hand sanitizer[4]. The product exceeded the FDA-indicated minimum performance standards for bacterial reduction in the test protocol as given in 21CFR333.470(b)(2), and also as modified from that protocol to omit the water rinse step (prior to glove-juice sampling) to emulate a leave-on application situation. Another study examined the performance of a benzalkonium chloride-containing, alcohol free sanitizer under 21CFR333.470(b)(2), without a water rinse[5]. The results again indicated that the test formulation exceeded the minimum performance standards given in the protocol.

The in vivo antimicrobial spectrum of benzalkonium chloride at the concentration listed in the 1994 TFM (0.1-0.13 wt %) is broad, and includes the organisms listed in the 1994 TFM protocol for effectiveness testing[8,12]. Numerous other submissions to this docket also support the antimicrobial spectrum of benzalkonium chloride. In addition, benzalkonium chloride is effective against a wide variety of viruses, including certain mixed-type viruses, and non-enveloped viruses[12-16]. In some

instances, benzalkonium chloride demonstrates a significantly greater virucidal activity than alcohol applications. An example of the utility of benzalkonium chloride-containing leave-on sanitizers was seen in the response to human coronavirus / SARS epidemic of 2003. As a means of limiting the spread of the virus from Asia, and to boost consumer confidence, several airlines sought effective leave-on sanitizer products to offer to clients returning from Asia. Alcohol-containing products were deemed unacceptable because of flammability issues. In contrast, a nonflammable benzalkonium chloride leave-on sanitizer was found to be very effective against human coronavirus[19]. It therefore was the leave-on sanitizer of choice for this important application.

A benzalkonium chloride-containing leave-on formulation was tested for effectiveness at reducing illness-related absenteeism in public and private schools. In one 10 week open-label, crossover study of 420 students[4] subjects using the leave-on sanitizer showed a 41.9% decrease in illness-related absence days compared to a group of students washing hands at-will with soap and water. Likewise, absence incidence decreased by 31.7%, consisting of a 44.2% and 50.2% decrease in incidence of gastrointestinal and respiratory-related illnesses, respectively. In a different 5 week double-blind, placebo-controlled study of 769 students, the group using the benzalkonium chloride-containing product experienced a 33% decrease in illness-related absenteeism[5]. The usefulness of a leave-on sanitizer containing benzalkonium chloride therefore has been clearly demonstrated. Because of the potential for misuse of alcohol-containing leave-on sanitzers, (e.g. as a fire accelerant,

or by intentional ingestion) we again assert that alcohol-free leave-on sanitizers are the only appropriate compositions for use in certain settings, such as public schools.

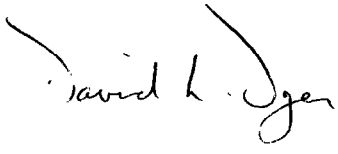
Resistance

Although bacterial resistance has been demonstrated for the active ingredient triclosan in a laboratory setting[17], field studies in which the product is used in non-laboratory environments (i.e. in "real-use" situations) have failed to substantiate these findings. The results of a recent study[18] showed a lack of antibiotic and antibacterial agent cross-resistance in target bacteria from the homes of antibacterial product users and nonusers, as well as increased prevalence of potential pathogens in nonuser homes. These findings refute the widely publicized, yet unsupported, hypotheses that use of antibacterial products facilitates the development of antibiotic resistance in bacteria from the home environment. Furthermore, at a joint meeting on January 22, 1997, FDA Advisory Committees agreed that the evidence to date indicated that topical antimicrobial wash products do not contribute to antimicrobial resistance, and recommended ongoing surveillance for the possible development of resistance to these agents. An excellent review on the issue of bacterial resistance to antibacterial sanitizers was also recently submitted by SDA to FDA in response to the reopening of the docket for comments.

Summary: The data submitted in this letter support the acceptance of benzalkonium chloride as Category I active ingredients for use in leave-on products in the future antiseptic monograph. We respectfully request that in consideration of this information, and in consideration of the other numerous submissions to this docket

supporting the safety and effectiveness of benzalkonium chloride as an active ingredient for topical antiseptic drug products, that FDA reclassify this ingredient as a Category I active for leave-on antiseptic/antibacterial applications.

Sincerely,



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