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August 28, 2003

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

Dear Sir/Madam:

Attached is a hard copy of the comments that were emailed to you on August 27, 2003 regarding the 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. (May29, 2003). [Docket No.75N-183H].

Thank you,

GOJO INDUSTRIES, INC.

Michael J. Dolan
Research and Development Vice President

75N-183H C74

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5620 '03

August 27, 2003

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

GOJO Industries, Inc. hereby submits these comments in response to the Food and Drug Administration's (FDA's) reopening of the administrative record regarding the tentative final monograph for Over-the-Counter (OTC) Health-Care Antiseptic Drug Products, 59 Fed. Reg. 31402 (June 17, 1994) (1994 TFM). **These comments address the safety and efficacy of benzalkonium chloride and benzethonium chloride as active antimicrobial agents in leave-on products (products used without water and that are not rinsed off the skin).**

SUMMARY:

The anticipated finalization of the 1994 TFM will be accompanied by a review of the safety and efficacy of the quaternary ammonium compounds (quats), benzalkonium chloride and benzethonium chloride. These active ingredients are listed as Category III drugs (available data are insufficient to classify as safe and effective, and further testing is required) in the 1994 TFM. We submit that benzalkonium chloride and benzethonium chloride lack sufficient data to be classified as safe and effective when specifically used in leave-on (no rinse) products according to the 1994 TFM.

We assert that:

- **Insufficient scientific evidence exists to approve either benzalkonium chloride or benzethonium chloride as Category I active ingredients for use in leave-on (non rinse) products in the 1994 TFM hand antiseptic categories.**

- **FDA should limit the use of benzalkonium chloride and benzethonium chloride for hand antiseptic use to only those products that are rinsed off the skin until such time as an extensive body of long term scientific evidence exists to demonstrate safety and effectiveness in non rinse, leave-on products.**

The potential for development of bacterial resistance, sensitization, irritation and other untoward effects due to the use of benzalkonium chloride and benzethonium chloride in leave-on products has been insufficiently addressed. The cumulative safety of these actives for leave-on antiseptic products requires additional scrutiny due to a use pattern that allows unlimited daily use for the lifetime of a user at home, at work and in the health care setting. An important point of reference is topical First Aid products. A survey conducted by Voss and Widmer (1997) suggested that nurses should wash 200 to 300 times per week. Based upon this use frequency, we estimate that nurses using quat containing, no rinse products would be exposed to 100 to 600 grams of quat per week, whereas a first aid antiseptic user would be exposed to approximately 10 to 40 grams of quat per week. In addition, leave-on products may expose the user to a higher initial concentration of the active and for an extended time. Finally, the potential for unchecked use and proliferation of these actives in leave-on products in the consumer market (as is already occurring) further multiplies the potential safety risks. The cumulative exposure to these actives across all applications and use patterns requires in-depth consideration by FDA.

BACKGROUND:

FDA has previously recognized limitations for the use of benzalkonium chloride and benzethonium chloride. Although quats have been briefly mentioned in several proposed monographs, the use of benzalkonium chloride and benzethonium chloride has not been granted Category I (generally recognized as safe and effective) status in any final OTC rule. Both have been proposed for Category I status in the tentative First Aid Antiseptic Monograph (FR 56(140):33644-33680, July 22, 1991) (1991 TFM). However, FDA mandated critical limits on the duration of use (i.e. 7 days), the frequency of use (e.g. one to three times per day), and the size of the treatment area (i.e. small cuts and scrapes). These limitations are not required by the 1994 TFM. The use range of 0.1% to 0.13% benzalkonium chloride and 0.1% to 0.2% benzethonium chloride has been drawn from this 1991 TFM, although the 1994 TFM does not clearly specify a range. Due to the aforementioned controlled use of quats in First Aid products, FDA should not rely upon the historical experience of First Aid products, as it clearly does not adequately simulate the dose or usage patterns of the 1994 TFM. This approved use pattern represents but a fraction of the exposure that could come from unrestricted, repeated daily use of a quat-based leave-on antiseptic.

FDA has previously recognized the paucity of data on file for benzalkonium chloride and benzethonium chloride, and in fact, recently requested additional absorption and systemic toxicity data in rodent and non-rodent species, skin wound repair comparison, contact dermatitis, and skin sensitization studies. Furthermore, there are insufficient data in the public domain to support the use of these actives in an unlimited, high-frequency use pattern which involves a direct leave-on application. .

IRRITATION / SENSITIZATION:

The attached references reveal the potential for irritation, sensitization and allergic response resulting from the use of benzalkonium chloride and other quaternary ammonium chlorides. A five-year study of healthcare workers showed a significant difference in dermatitis resulting from exposure to benzalkonium chloride compared to non-healthcare workers ($p=0.046$) (Shaffer et al. 2000). In addition,

quaternary ammonium chlorides have demonstrated potential for inhibition of wound healing and tissue injury when used as antiseptics (Branemark, 1966, 1967). Prolonged exposure to these actives due to direct "leave-on" application may increase exposure, and thus health effects, as much as ten-fold.

The 2002 Cosmetic Ingredient Review (CIR) Compendium considers benzalkonium chloride "cosmetic" formulations above 0.1% to be unsafe; thus the 1994 TFM formulation ranges are inconsistent with more recent national safety guidelines. Although less safety and efficacy information exists for benzethonium chloride, the 2002 CIR Compendium lists benzethonium chloride formulations as safe for use in cosmetics at or below 0.5%. Based upon the CIR, benzethonium chloride formulations above 0.5% would not be safe for use on human skin. However, the Cosmetic Ingredient Review has listed the benzethonium chloride group as requiring re-evaluation due to the age of the submitted studies (early 1980s). As the CIR review was based upon the application of cosmetics, 1994 TFM use patterns would most likely necessitate further reductions in the CIR cut-off values. **Benzalkonium chloride and benzethonium chloride have not been proven safe and effective for use in leave-on products under the extensive use scenario covered by the 1994 TFM. Current 1994 TFM concentration ranges for benzalkonium chloride are unsafe according to the 2002 CIR Compendium.**

ANTIMICROBIAL EFFECTIVENESS:

The efficacy of quaternary ammonium compounds may be severely compromised during formulation and use. Benzalkonium chloride and benzethonium chloride may be neutralized by anionic or nonionic surfactants, hard water, proteins and other moieties. Special expertise is required when formulating to avoid neutralization of these active ingredients and to carefully balance the need for fast, broad spectrum antimicrobial activity with low irritation. Little published data exist to demonstrate the effectiveness, according to 1994 TFM testing standards, of leave-on formulations based on benzalkonium and benzethonium chloride across the proposed concentration range. **Thus, we conclude that**

benzalkonium and benzethonium chloride have not been proven to be generally recognized as effective for use in leave-on products in the future monograph.

MICROBIAL SKIN FLORA

Published scientific studies have identified concerns for the selection and proliferation of quat-resistant bacteria and accompanying antibiotic cross-resistance (Adair, 1969, 1971; Gilbert, 2003; Joynson, 2002; Loughlin, 2002). Although these studies are mainly laboratory evaluations, many key thought leaders have begun to express concern over these findings. A.D. Russell, the lead academician in this field, stated as early as 1998, "Extensive use of cationic biocides [benzalkonium chloride and benzethonium chloride] could lead to the selection of staphylococcal strains showing resistance to both antibiotics and biocides..." (Russell, 1998). No studies have been published to date exploring the short or long term impact of the use of benzalkonium chloride and benzethonium chloride on the ecology of the skin flora and the resistance profiles of its members. Horn's and Larson's elucidations of the changes in the ecology of the skin flora of healthcare workers further emphasize the concern that increased use of benzalkonium chloride and benzethonium chloride may contribute to a shift in resident skin flora, specifically selecting for Gram negative strains due to the unique innate resistance of these strains to quat compounds or biocide/antibiotic resistant *Staphylococci* (Horn, 1988; Larson, 1998). **Benzalkonium and benzethonium chloride should not be approved as Category I active ingredients for unlimited, high-frequency use in leave-on products until further investigation elucidates their potential to alter the ecology as well as the biocide and antibiotic resistance profiles of human skin flora.**

In summary, FDA should not approve benzalkonium chloride and benzethonium chloride as Category I active ingredients for use in leave-on products in the future antiseptic monograph. Benzalkonium and benzethonium chloride have not been proven safe and effective for use in leave-on products. FDA should limit the use of benzalkonium and benzethonium chloride for antiseptic use to

rinse-off products until an extensive body of long term scientific evidence exists to demonstrate safety and effectiveness for leave-on products.

Respectfully Submitted,

GOJO INDUSTRIES, INC.

Michael J. Dolan
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