



THE **DIAL** CORPORATION

August 27, 2003

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Dockets Management Branch  
Docket No. 75N-183H  
Food and Drug Administration (HFA-305)  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

Re: Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health Care Antiseptic Drug Products; Re-opening of the Administrative Record; Docket No. 75N-183H

Dear Sir or Madam:

The Dial Corporation (Dial) would like to take this opportunity to commend the Food and Drug Administration (FDA) on the reopening of the administrative record. Dial hereby submits the following comments to the above referenced rulemaking. These comments supplement a previous submission<sup>1</sup> that The Dial Corporation has made to the FDA on this rulemaking. These comments further supplement submissions made by The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association<sup>2</sup> (Industry Coalition) as well as the Ciba Specialty Chemicals Company<sup>3</sup> and the Bayer Chemicals Corporation<sup>4</sup>. These submissions demonstrate the continuous effort Industry has undertaken to establish safe and efficacious products. To ensure that FDA's rulemaking is complete, Dial requests that FDA continue to accept into the administrative record data and information relevant to the safety and effectiveness of ingredients after August 27, 2003. As per the Industry Coalition submission, Dial encourages FDA, at the very least, to defer final action on Category II and Category III ingredients that are being studied or may be dependent upon Agency feedback.

<sup>1</sup>Comments to the TFM for Topical Antimicrobial Drug Products for Over-the-Counter Use, The Dial Corporation, June 15, 1995.

<sup>2</sup>Proposal of the Healthcare Continuum Model, June 15, 1995; Compilation of efficacy data, December 13 1995 and March 11, 1996; Finished product efficacy testing, September 29, 1999; Citizen's Petition for labeling, April 2, 2001; Citizen's Petition on monograph flexibility, June 1, 2001; Citizen's Petition on surrogate endpoint testing, November 28, 2001; Citizen's Petition supporting healthcare professional products, August 6, 2001; Citizen's petition requesting anti-viral claims, January 17, 2003; Citizens Petition in support of consumer products, May 23, 2003.

<sup>3</sup>Comments to the TFM for Topical Antimicrobial Drug Products for Over-the-Counter Use, Ciba-Geigy Corporation, June 15, 1995; Citizen's Petition providing data support for triclosan, January 15, 2002.

<sup>4</sup>Citizen's Petition providing data support for triclocarban, Bayer Corporation, December 28, 2002; Supplemental data to the TFM docket, August 26, 2003.

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In this submission The Dial Corporation provides information on the efficacy of some Category III ingredients, the test methods used to assess efficacy, specific antimicrobial efficacy/benefit studies, and the labeling of topical antimicrobial drug products.

A summary of The Dial Corporation's submission and information follows:

- Based on previously submitted data, as well as new data contained herein, triclosan should be considered as a Category I ingredient for both safety and efficacy up to 1% for use in Health Care Personnel Hand Washes and Antiseptic Hand Washes.
- Based on previously submitted data, as well as new data submitted by the Bayer Chemicals Corporation<sup>4</sup> triclocarban should be considered as a Category I ingredient for both safety and efficacy up to 1.5% for use in Health Care Personnel Hand Washes and Antiseptic Hand Washes.
- The standardization of efficacy test methods by incorporating voluntary consensus standards, such as ASTM methods, will ensure accurate, reproducible test results are obtained.
- Topical antimicrobial drug products provide a significant hygienic benefit beyond that provided by plain soap and water.
- Topical antimicrobial drug products demonstrating antimicrobial efficacy linked to deodorancy support antimicrobial deodorant claims as OTC-drugs.
- Based on consumer understanding of antiseptic and antibacterial/antimicrobial terminology, appropriate OTC drug product labeling for both professional and consumer products should be provided (re: Statement of Identity, Warnings, Reduced Content and Format Requirements).

## **I. Certain Category III Ingredients**

### **A. Efficacy of Triclosan**

Ciba Specialty Chemicals Company (Ciba), the drug manufacturer of triclosan, has previously submitted efficacy data to the FDA on this rulemaking since 1994 (December 14, 1995; February 11, 2002) in support of triclosan as a Category I ingredient for health care professional products. The Dial Corporation supports the data provided to the Agency by Ciba. Supplemental efficacy data on a health care personnel hand wash formulation containing both 0.45% and 1% triclosan are provided in this submission. The Dial Corporation

currently markets a healthcare personnel hand wash, for healthcare professional use, containing triclosan as the active ingredient.

Fuls, *et al.* (2003) demonstrated that a properly formulated topical antimicrobial hand wash containing 1% triclosan provided efficacy exceeding that achieved by a 4% chlorhexidine gluconate hand wash in a standardized health care personnel hand wash test (ASTM E1174). The 1% triclosan containing formula achieved a 3.78 log<sub>10</sub> reduction following a single wash, and a 4.07 log<sub>10</sub> reduction following 10 subsequent washes. This compared to a 2.54, and 3.72 log<sub>10</sub> reductions for the chlorhexidine gluconate formula. The detailed test report and protocol are provided in Attachment 1 (HTR Study No. 00-105790-11). Attachment 2 (HTR Study No. 01-109083-11) shows the results of an additional Healthcare Personnel Hand Wash study utilizing a 0.45% triclosan formulation. This formulation achieved a 3.47 log<sub>10</sub> reduction following a single wash, and a 3.58 log<sub>10</sub> reduction following 10 subsequent washes. These data compare favorably with data previously submitted to the docket by Ciba Specialty Chemicals Company (February 11, 2002) that demonstrated 3.73 and 3.97 log<sub>10</sub> reductions for a formula containing 0.3 % triclosan and 3.63 and 3.79 log<sub>10</sub> reductions for a formulation containing 0.6 % triclosan.

The above referenced effectiveness of triclosan containing topical formulations can best be understood by the chemistry of such formulas. A paper describing the physiochemical parameters affecting the efficacy of triclosan was presented at the 2002 National Meeting of the American Chemical Society (ACS). It is included in this submission as Attachment 3, and is in preparation for publication.

#### **B. Efficacy of Triclocarban**

The Bayer Chemicals Corporation, the drug manufacturer of triclocarban, has previously submitted in a Citizens Petition to the docket, efficacy data in support of triclocarban at 1.5% as a Category I ingredient (December 28, 2002). The Dial Corporation supports the data provided to the FDA by Bayer Chemicals Corporation. Supplemental data submitted to the Docket by Bayer (August 26, 2003) further supports the use of triclocarban at 0.7% as a Category I ingredient for use as a health care personnel hand wash or an antiseptic hand wash.

Although the evaluation of health care personnel hand washes through *in vivo* testing is traditionally carried out using a Gram-negative surrogate organism (either *Serratia marcescens* or *Escherichia coli*) the use of a relevant Gram-positive organism (*Staphylococcus aureus*) is no less valid. The available literature, as well as hospital infection control records, have documented

numerous instances of nosocomial infections traced to the spread of *S. aureus*. The importance of controlling the spread of *S. aureus* cannot be underestimated.

The new data specifically demonstrate the superiority of a triclocarban containing hand wash at de-germing the hands of the Gram-positive microorganism, *S. aureus*. In a health care personnel hand wash test (ASTM E1174), a 0.7% triclocarban containing product achieved a 2.82 log<sub>10</sub> reduction following a single wash and a 3.09 log<sub>10</sub> reduction following 10 subsequent washes. This compares to 1.84 and 1.99 log<sub>10</sub> reductions for the placebo product, and 2.25 and 2.38 log<sub>10</sub> reductions for a 4% chlorhexidine gluconate product.

## II. Standardization of Test Methods

The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association (Industry Coalition) have previously submitted information to the docket (September 16, 1999; November 28, 2001) on the importance of using standardized test methods for the evaluation of topical antimicrobial drug products. The Dial Corporation fully supports the Industry Coalition's proposals and recommendations on testing.

In the September 16, 1999 submission, the Industry Coalition stated that *Escherichia coli* could be used as an alternate test organism in the ASTM E1174 Health Care Personnel Hand Wash test. The Dial Corporation, in this submission to the docket is providing comparative data on the use of *E. coli* and *S. marcescens* as marker organisms when both triclosan and chlorhexidine gluconate containing formulations are tested by ASTM E1174. Fischler, *et al* (2003) demonstrated that comparable results could be achieved with both 1% triclosan and 4% chlorhexidine gluconate formulations using either *E. coli* or *S. marcescens* as the marker organisms, 3.78 vs. 3.79 log<sub>10</sub> reduction and 4.07 vs. 4.05 log<sub>10</sub> with the triclosan formula following a single and 10 subsequent washes respectively. For the 4% chlorhexidine gluconate formula the comparative log<sub>10</sub> reductions were 2.54 vs. 2.86 and 3.78 vs. 4.22. The detailed test report and protocol of the *E. coli* test is provided as Attachment 4 (HTR Study No. 00-105821-11). The test formulations are the same as those previously referenced in Attachment 1.

## IV. Antimicrobial Benefits

### A. Hand-to-Hand Transmission

The transmission of transient microorganisms from one person to another plays a significant role in the direct transmission of disease. A reduction in the transfer of microorganisms within a population would have a potentially

significant impact on the reduction of nosocomial infection, as well as an overall positive effect on infections in general. Reducing the transmission of microorganisms provides a valuable benefit in improving the public health, and should therefore be considered in the evaluation topical antimicrobial drug products. The current standard method for the evaluation of the reduction of transient microorganisms following hand washing is the ASTM E1174 test method, and has been extensively referenced in this document. Methods to evaluate the subsequent transfer of microorganisms from one person to another have not been well studied.

The Dial Corporation is providing as part of our submission to the docket two (2) studies that examine this hand-to-hand transfer utilizing a modified Cup Scrub procedure (Attachments 5 and 6). The efficacy of a 0.45% triclosan containing hand wash formulation was compared to a non-antimicrobial hand wash formulation. Attachment 4 (CRL Study No. 03-121608-123) contains the details of a pilot study utilizing a total of twelve (12) subjects (six per product). Attachment 5 (CRL Study No. 03-121617-123) contains the details of a study using the same formulations but utilizing a total of thirty (30) subjects, fifteen (15) per product. The results of both studies show significant differences in both in-situ post wash bacterial reduction, as well as significant differences in the numbers of post wash bacteria transferred from one hand to another when comparing the antimicrobial and non-antimicrobial formulations.

## **B. Antibacterial Deodorancy**

The FDA stated in comment 27 of the Tentative Final Monograph for Topical Antimicrobial Drug Products (59 FR 31440) in discussing antimicrobial deodorancy claims that "Specific testing for antimicrobial claims for deodorancy has not yet been developed. The agency intends to review any comments or methods submitted for such a purpose in response to this publication and invites comments and data on this topic." In response to the agency's comment, The Dial Corporation is supplying as part of this submission to the docket a study demonstrating the antimicrobial efficacy of an antibacterial soap preparation, linked specifically to its deodorancy. This correlation supports antimicrobial deodorant products as OTC-drugs.

In brief, under conditions of a standard axillary deodorancy evaluation, a positive relationship was demonstrated between treatment of the axilla with an antibacterial soap (containing 0.78% triclocarban or TCC) and a reduction in axillary malodor and anaerobic microflora. A similar positive relationship was not demonstrated with treatment of the axilla with a placebo soap or tap water. Statistically significant reductions in malodor and total anaerobic bacteria were demonstrated 8 hours following the final treatment of the axillae with

antibacterial soap. Some slight reductions in malodor and total anaerobic bacteria were demonstrated with placebo bar and tap water, but neither treatment resulted in statistically significant decreases from baseline observations.

A summary of the study findings and the report is provided in Attachment 7. (The Report for Deodorant Efficacy Study Including Axillary Microbial Flora Quantitation, Hill Top Research, Inc, HTR Study No. 03-121863-109).

## V. OTC Labeling

### Statement of Identity - Antiseptic vs. Antibacterial Terminology

Based upon The Dial Corporation's market research study conducted in 1995 and submitted to the FDA (Attachment 8), the term antiseptic is very confusing to the typical consumer of body wash and hand wash products and is inconsistent with the current marketing practices for these products. The Study consisted of interviews with eight hundred consumers (n=800) in a telephone survey. Consumers were asked to define the terms antibacterial and antiseptic. The summary results of the Study are as follows:

- Antibacterial was significantly more likely to be defined as "kills bacteria" and "fights/removes germs/bacteria."
- Antiseptic was described significantly more often as "kills germs," "medicinal" (particularly "fights infections/sterilizes"), and "sanitized/sterilized." The consumer perception of antiseptic products is associated with medicinal, sterilized and infection fighting products. Therefore, the antiseptic terminology should be reserved for professional healthcare and food handler product categories of the Health-Care Continuum Model. The terms antimicrobial and antibacterial more precisely convey and are understood by the typical consumer as the key benefit and purpose of the consumer body wash and hand wash categories. These terms therefore should be used for clear and concise (non-misleading) labeling for the consumer topical product categories.

### Warning Statement for Consumer Products - "Keep out of reach of children"

As stated in 21 CFR 330.1(g), all OTC drug products must include the general warning "Keep out of reach of children." The statement "Keep out of reach of children," for consumer hand wash and body wash products is confusing, given that the intended use of safe and effective topical antibacterial drug products is personal hygiene for the entire family. The entire family population, which includes children, uses topical antibacterial products on a daily basis as part of a good hygiene

program. Therefore, Dial recommends that the statement be modified to read,  
“Keep out of reach of children except under adult supervision.”

OTC Drug Facts Labeling – Reduced content and format requirements

The Dial Corporation produces numerous hand wash and body wash package sizes for the professional and the consumer markets from very small convenient sizes (1.5, 4.0 fluid ounce) to large refill containers (more than 1 gallon). Based on the small individual package sizes for both the professional and consumer markets, it has proven difficult to meet the requirements under 21 CFR 201.66 on the smaller sizes even under 21 CFR 201.66(d)(10). Dial’s smaller packages provide consumers and professionals hygiene benefits in an easy-to-use form. Dial encourages FDA to provide for reduced content and format alternatives for small packages of hand wash and body wash products.

Sincerely yours,



Elizabeth A. Dail  
Director  
Product Safety, Regulatory Affairs & Microbiology

## References

Fischler, G E; J L Fuls; G K Mulberry. 2003. *The use of E. coli as an alternate test organism in the ASTM E1174 health care personnel hand wash method.* American Society for Microbiology 103rd Annual Meeting, Washington, DC Poster Q-287.

Fuls, J L; G E Fischler; G K Mulberry; K A Baxter; A Brady. 2003. *Antimicrobial efficacy of activated 2,4,-trichloro-2'-hydroxy diphenyl ether (Triclosan) in surfactant based formulations.* American Society for Microbiology 103<sup>rd</sup> Annual Meeting, Washington, DC. Poster Q-277