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

Re: Docket No. 75N-183H
Comments in response to Federal Register Notice, May 29, 2003, page 32003

Dear Sir/Madam:

Pursuant to the above-referenced Federal Register Notice, Healthpoint, Ltd. submits the following comments, in triplicate, concerning the proposed rulemaking for OTC health-care antiseptic drug products and data and information submitted after August 17, 1995 to the administrative record for the Tentative Final Monograph for Health-care Antiseptic Drug Products published June 17, 1994 ("TFM"). The prompt publishing of a final monograph is strongly urged to end the confusion in the marketplace as to the criteria for such products and to provide the maximum safety and efficacy for healthcare personnel and patients. Healthpoint's comments for your consideration are as follows:

1. The TFM *in vivo* $\log_{10}$ antimicrobial reduction criteria are achievable with products formulated with alcohol and other compounds to provide persistence, since it is well known that alcohol alone does not demonstrate the required $\log_{10}$ microbial reductions (See TFM at page 31412.). To provide products with the maximum safety and efficacy and to reduce antimicrobial contamination and infection in the healthcare setting, the *in vivo* criteria as set forth in the TFM should be finalized. Products are on the market that meet the TFM requirements. For example, the data provided in Appendix A are test results for a product that has been formulated to meet the TFM requirements for healthcare personnel handwash and study results demonstrating a product's persistence and residual effect exceeding the TFM requirements. In addition, the technical bulletin in Appendix B is an example of a product that has been formulated to meet the TFM requirements for surgical scrub, the technical bulletin in Appendix C is an example of a product formulated to meet the TFM requirements for patient preoperative skin preparation, and the reprints in Appendix D provide additional pertinent information. The data provided in these Appendices demonstrate that

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alcohol-based products can be formulated to have persistence that meets or exceeds the TFM requirements. To reduce or eliminate the requirement for antimicrobial persistence would be punitive to those who have successfully complied with the proposed regulation and could place in jeopardy both the users and the patients if less efficacious products were employed.

2. The TFM should be modified to include either denatured or nondenatured alcohol 60-95% as active ingredients. Nondenatured alcohol (alcohol, U.S.P.) would have the same safety and efficacy profile in these products as denatured alcohol.

3. The *in vitro* requirement that the minimum inhibition concentration (MIC) panel be performed with approximately 1100 isolates representing numerous species is onerous and should be reconsidered. Adequate numbers of ATCC strains and clinical isolates may not be readily available for all of the required test organisms. An appropriate number would be a total of 600 strains and isolates.

4. The required alcohol product dilution in the TFM MIC procedure results in data that can be misleading, and this assay should be eliminated from the testing requirements. For alcohol-based products, dilutions of the product are not appropriate when the products are used at full strength without dilution. Considerable data fluctuation exists with the TFM MIC test procedure, as it is based upon sequential dilutions of the product, the active, and the vehicle that are meant to be effective at a specific concentration. This is particularly true for waterless healthcare personnel handwash and surgical scrub formulations. There is much data to support the premise that the dilution of alcohols drastically reduces their antimicrobial effectiveness and is not representative of their clinical use.[1, 2] It should also be noted that alcohol-based products in the *in vivo* and *in vitro* tests are neutralized solely through dilution. Under the current TFM, if during the course of testing a specific antimicrobial agent, a three to five dilution difference in the MICs of some strains is discovered, it is difficult to determine how the information is to be viewed, i.e., investigation of the possibility of an isolate/strain developing resistance to the active ingredient or a simple variation associated with the test procedure. This could be eliminated by a modification of the procedure to delete the need for dilutions of alcohol-based products.

5. Since the use of antimicrobial products with low levels of activity may provide conditions for developing drug resistance, a formal protocol for assessing microbial resistance to these compounds should be developed and employed. However, consideration should be given to protocol modifications that are germane to the specific active ingredient. For example, alcohol is known to not induce point mutations that lead to resistance, while the same cannot be stated for Triclosan, as related to certain strains of *Escherichia coli*.[3, 4, 7]

6. The Time-kill study as described in the TFM is an excellent test, as it provides valuable data regarding the true antimicrobial power of the product. As the name implies, the test determines the time from less than a minute to multiple minutes

required for the product to kill the microbial agent. Microbial death, as measured by the Time-kill test, is a better indicator and a more desirable outcome of skin antisepsis than is nonquantified microbial stasis. The quantity of product required to kill (as determined by the MIC) is not a critical factor as long as the test is performed in a manner that mimics product application instructions per label directions. If the number of required organisms for the MIC is decreased or the MIC is eliminated for certain products, the number of test organisms for the Time-kill study could be increased to approximately 600.

7. The antimicrobial range assessment should be combined with the Time-kill studies as, again, microbial death is a more desirable outcome of product use and skin antisepsis. This test should be limited to only those organisms that are frankly pathogenic, may be opportunistic in the immunocompromised host, or likely to be spread/transmitted by the healthcare provider to the patient. This assay should include selected anaerobic and aerobic bacteria, known drug-resistant bacteria, yeasts, fungi, and viruses. In this manner, the true antimicrobial range of the product would be elucidated.

8. Chlorhexidine gluconate (CHG) should not be included as a Category I active ingredient in this OTC Monograph, due to known toxic effects associated with it, the pH dependent nature of it antimicrobial action, and the potential for inactivation by anionic materials commonly found in other products such as soaps, moisturizers, and lotions. [5, 6, 11-16, 18]

9. Benzethonium Chloride should not be included as a Category I active ingredient because of reduced antimicrobial efficacy in MIC and time-kill data, formulation issues, compatibility issues similar to those of CHG, and known problems associated with antimicrobial resistance and skin irritation. [5, 6, 17]

10. Triclosan should not be included as a Category I active ingredient. A single point mutation in the bacterium *Escherichia coli* has resulted in the development of resistance to Triclosan. Therefore, it should be marketed through the drug approval process rather than as an antimicrobial agent in the TFM.[3, 4, 7] The poor performance of a product containing 0.5% Triclosan is shown in the data in Appendix A. In the study presented, the Triclosan product provided little immediate antimicrobial action, and antimicrobial persistence was not observed. The documented resistance to Triclosan by a common bacterium coupled with marginal efficacy make this antimicrobial unacceptable for inclusion in Category I. in the TFM.

11. PCMX should not be included as a Category I active ingredient due to developing resistance in *Pseudomonas aeruginosa.* [5,6]

12. CDC[8] and AORN[9] guidelines have supported the use of alcohol-based surgical scrub products.

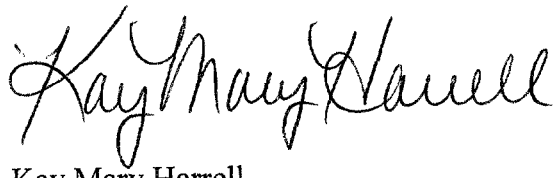
13. The proposed labeling directions for all TFM product categories should clearly provide that the directions reflect the manner in which the products were tested, e.g., "(c) Directions. The labeling of the product contains statements, under the heading "Directions," that reflect the conditions under when the product was tested according to section 333.470xx or: (1).... Suggested revisions for the Directions sections of the monograph are provided in Appendix F.

14. Additional labeling and testing sections should be added to the Patient Preoperative Skin Preparation based upon recent CDC recommendations to include a preoperative skin preparation body wash for surgical patients.[10] The suggested labeling section is as follows: (3) For products containing any ingredient in 333.412(b) or (c) that are intended to be used as a body wash. "Wash in the shower or bath [Insert method of application when tested according to 333.470xx, e.g., X times before your surgical procedure.]" If appropriate, add "For each wash, wet your entire body. Pour approximately Yml into your hand and rub over the entire body, paying particular attention to the site of the surgery. Rinse and repeat." The body wash should meet the current patient preoperative skin preparation testing criteria.

The references cited above are listed in the attached Appendix E.

Thank you for your consideration of these comments in support of a final monograph for healthcare antiseptic drug products.

Very truly yours,



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