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

Please accept 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 performance criteria proposed for health-care antiseptic drug products, which threaten the availability to the healthcare industry of alcohol-based hand disinfectants having demonstrated efficacy and health benefits. Specifically, these comments are directed to products that fall under the Antiseptic Handwash/Health-Care Personnel Handwash category (§333.410(a)), and not those in the Surgical Hand Scrub or Patient Preoperative Skin Preparation categories.

SUMMARY:

Ethyl and isopropyl alcohol have long been established as safe and efficacious for use as antiseptic agents. Indeed, the 1994 TFM recognizes 60-95% alcohol as Safe and Effective (Category I) for skin antisepsis. In spite of the well documented benefits of alcohol-based hand sanitizers/rinses/rubs, finalization of the 1994 TFM in its current form would effectively remove from the market many of the very products that have been used in recent years to demonstrate the safety and clinical effectiveness of alcohol hand disinfectants. In addition, the 1994 TFM proposal would impose on the market reformulated products containing supplemental antimicrobial

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ingredients; such formulas have unproven clinical benefit and present several potential risk concerns.

The 1994 TFM creates an inherently conflicting scenario for alcohol-based disinfectants that are designed for routine, rapid hand disinfection. The Health Care Personnel Handwash Test methodology and performance criteria require products to exhibit a cumulative ("persistent" or "residual") antimicrobial effect, while at the same time 1994 TFM Comments acknowledge the lack of such an effect by alcohol, a Category I active ingredient. This inconsistency will result in the failure of most existing alcohol-based hand sanitizers to pass 1994 TFM efficacy standards. Most products that do pass the standards contain, or will be reformulated to contain additional biocidal ingredients to provide the cumulative effect. The risk/benefit of this additional antimicrobial chemical(s) is not sufficiently demonstrated to be a mandated requirement for products. Further, alcohol-based hand antiseptics in this category are intended for frequent, rapid skin degerming and a cumulative/persistent effect is not a necessary attribute.

The 1994 TFM does not link test methods and performance criteria to the demonstrated benefits of currently-marketed alcohol hand disinfectants. A significant body of scientific evidence has been generated since the 1994 TFM issued, and this needs to be incorporated into any future Final Monograph. I am requesting that FDA consider accommodating this need by modifying the performance standards to eliminate the requirement for a persistent effect.

The key points discussed in this submission are:

- The safety and effectiveness of currently-marketed OTC alcohol-based hand antiseptics are supported by a body of peer-reviewed scientific evidence.

- The 1994 TFM testing methodology and performance criteria for the Health-Care Personnel Handwash are contradictory to the concept and function of alcohol-based hand antiseptics intended for rapid, frequent degerming of hands of healthcare workers in healthcare settings. *In fact, the requirement for demonstration of a persistent effect could mislead healthcare workers into thinking that application between each set of patient contacts is not necessary.*

- Any future Final Monograph for Health-Care Antiseptics should incorporate changes that address the inconsistencies in the 1994 TFM and provide test methodology and performance criteria that correlate with the proven safety and efficacy profiles of currently marketed alcohol hand antiseptic products.

- The FDA provided input throughout the development of 2002 CDC "Guideline for Hand Hygiene in Health-Care Settings" (Boyce, 2002) via the FDA liaison to HICPAC. Additionally, FDA and HICPAC agreed upon the final language and recommendations of this guideline during a series of teleconferences conducted prior to publication of the guideline. Therefore, *in the absence of new scientific data, it would be inconsistent for the FDA to take action that would jeopardize the implementation of the previously agreed upon recommendations for the use of hand hygiene products.*

ALCOHOL-BASED HAND ANTISEPTICS OFFER DEMONSTRATED HEALTH BENEFITS

The 1994 TFM recognizes 60-95% alcohol as Safe and Effective (Category I) for skin antisepsis when used as an antiseptic handwash or health-care personnel handwash active ingredient (§330.410(a). Since that time, product innovation and scientific evidence have combined to establish alcohol-based hand antiseptics (notably those based on ethanol), as preferred and valuable tools to improve public health. A range of products are available to meet the needs of today's widespread healthcare environments.

Alcohol hand antiseptics (variously referred to as hand sanitizers, rubs, rinses, gels) demonstrate rapid, broad spectrum *in vitro* and *in vivo* antimicrobial efficacy (Ali, 2001; SDA/CTFA , 2001). Numerous studies in healthcare settings (summarized in SDA/CTFA Coalition, 2001 and Boyce, 2002; Fendler, 2002; Hilburn, 2003; Trick, 2003) and community settings (Guinan, 2000; Hammond, 2002) have demonstrated the effectiveness of currently marketed alcohol-based antiseptics to reduce the transmission of pathogens and to reduce disease rates. Furthermore, alcohol hand sanitizers have been shown to provide exceptional timesaving in healthcare settings and to encourage consistent, high frequency hand hygiene compliance resulting in further disease mitigation (Bischoff, 2002; Girard, 2001; Harbath, 2002; Hugonnet, 2002; Pittet, 2000; Pittet, 2001). The scientific evidence surrounding alcohol antiseptics was extensively reviewed by a joint committee of CDC, SHEA, APIC, HICPAC, and IDSA and is summarized in the 2002 CDC "Guideline for Hand Hygiene in Health-Care Settings" (Boyce, 2002; this document has been submitted to the TFM docket). In this guideline, it was concluded that "alcohol-based hand rubs are the most efficacious agents for reducing the number of bacteria on the hands of personnel.." The guideline further recommends alcohol-based hand rubs "for routine decontamination of hands for all clinical indications (except when hands are visibly soiled) and as one of the options for surgical hand hygiene." In a series of teleconferences that included the FDA,

representatives of HICPAC and CDC, and the FDA approved the language and recommendations in that guideline.

THE 1994 TFM TEST METOD AND PERFORMANCE CRITERIA ARE CONTRADICTORY TO THE INTENDED USE OF ALCOHOL-BASED HAND ANTISEPTIC WASHES

Alcohol-based antiseptic handwash products are intended for frequent, repeated use by healthcare workers to rapidly reduce the level of transient skin microorganisms. As such, the most important performance factors are speed of action and spectrum of activity. A persistent, or cumulative, effect is not a necessary requirement.

The *in vivo* test for effectiveness of a health-care personnel handwash described in the 1994 TFM (§330.470(b)(2)) is a modification of the American Society for Testing and Materials (ASTM) Method ASTM E1174. The 1994 TFM performance criteria (§333.470(b)(2)(iii), p.31448) using this test are a 2 $\log_{10}$ reduction in the test organism after the first wash and a 3 $\log_{10}$ reduction after the tenth wash. Thus, the 1994 TFM requires a product to have a persistent effect. At the same time, the TFM Comments record (p.31412) "Because it is well established that alcohol alone does not provide persistence, the agency notes that a preservative agent in the vehicle provided the persistent effect to maintain reduction in the baseline number of bacteria..."

The combination of the 1994 TFM test method/performance criteria and the non persistence of alcohol create a situation where alcohol hand sanitizers would be required to have a secondary biocide in the formula. There are no demonstrated clinical benefits to the incorporation of secondary, persistent/cumulative antimicrobial ingredients into alcohol-based hand disinfectants designed for frequent, rapid hand hygiene. On the contrary, there are important potential downsides and significant risk/benefit considerations. Non-rinse ("waterless") products pose higher dermal exposure levels to the residual biocides than traditional handwashing compounds, have unknown long term effects upon natural skin flora, pose at least a theoretical risk of increased odds of the development of biocide-resistant organisms, and may convey a false sense of security to users based upon the belief that a "long lasting" formula provides a type of on-going barrier protection.

The usage pattern for alcohol-based hand antiseptics requires rapid, broad spectrum kill under frequent application, a representative situation being healthcare personnel use of the product immediately before and after interacting with a patient. Thus, the most relevant sampling time for a hand sanitizer is after the first product usage. The requirement for a cumulative

effect after multiple washes is not appropriate for alcohol, which evaporates from the hands. Further, it is inappropriate to require that the caregiver use the product repeatedly to obtain efficacy. The first patient of the day should benefit as much as the last.

A FINAL MONOGRAPH FOR HEALTH-CARE ANTISEPTICS SHOULD INCORPORATE CHANGES THAT ADDRESS THE INCONSISTENCIES IN THE 1994 TFM RELATED TO ALCOHOL HAND ANTISEPTICS

In spite of the well documented benefits of alcohol-based hand sanitizers, finalization of the 1994 TFM in its current form will effectively remove a majority of the currently available products from the market. This is inappropriate, runs counter to public health concerns, and will impose unnecessary restrictions on health-care institutions. Furthermore, this scenario will almost certainly result in reformulated products with less proven risk/benefit considerations.

For these reasons, it is imperative that any future Final Monograph for Health-Care Antiseptics correct the inherent conflicts in the 1994 TFM. Fortunately, this will be relatively easy to accomplish by simple elimination of the persistence/cumulative requirement for alcohol hand antiseptics. The test performance criteria should be limited to the first wash, thereby correlating with actual conditions of use and the established history of current product effectiveness.

Sincerely,

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