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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:

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 proposed *in vivo* test methodology and performance criteria for antiseptic handwash and healthcare personnel handwash (HCPHW) products (§330.470(b)(2)), which specifically threaten the availability of alcohol-based hand sanitizers for use in professional healthcare as well as consumer and other community settings.

SUMMARY:

The safety and efficacy of alcohol for use as a topical antiseptic are well established. Outcome studies executed in both healthcare and non-professional settings have demonstrated that alcohol-based hand antiseptics "used without water" (also referred to as hand sanitizers/ hand rubs/ hand rinses/ hand

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gels) are effective at reducing the spread of disease. Furthermore, the 1994 TFM recognized the safety and efficacy of 60-95% alcohol (ethanol) by establishing it as a Category I active, i.e. "generally recognized as safe and effective" for use in all three skin antiseptic product categories (antiseptic handwash/HCPHW, patient pre-operative skin preparation, and surgical scrub). In spite of this recognition, finalization of the 1994 TFM in its current form threatens to remove from the market many of the products that have been used to demonstrate the safety and clinical effectiveness of alcohol-based hand sanitizers.

The specific threat to alcohol-based hand sanitizers arises from methodology/performance criteria proposed in the 1994 TFM that do not reflect the use and performance of products demonstrated to reduce the spread of infection. The 1994 TFM test methodology and performance criteria essentially require HCPHW products to exhibit a cumulative antimicrobial effect, whereas the TFM comments (p.31412) acknowledge the absence of such an effect from alcohol. If a final monograph were to adopt the 1994 TFM performance criteria, it is estimated that the majority of alcohol-based hand sanitizers would be removed from the market (SDA/CTFA, 2001). The FDA is therefore encouraged to incorporate into any Final Monograph appropriate changes to the HCPHW methodology and performance criteria to be reflective of product efficacy and to ensure availability of safe and efficacious alcohol-based hand sanitizers.

The key points that are discussed in this submission are:

I. **Alcohol-based hand sanitizers have been proven to decrease disease transmission and increase hand-hygiene compliance in both healthcare and non-professional settings.**

II. **The healthcare personnel handwash test methodology and performance criteria proposed in the 1994 TFM are not appropriate to define the antimicrobial effectiveness of alcohol-based hand sanitizers.**

   a. **The HCPHW performance criteria do not reflect the antimicrobial efficacy of currently marketed products with clinically-proven effectiveness.**

   b. **The efficacy of HCPHW products should be demonstrated after a single use. The demonstration of a cumulative effect following multiple applications should not be required.**

   c. **The efficacy of HCPHW products should be determined by comparison to the baseline survival of the marker organism. Comparison to a baseline wash performed with a non-antimicrobial soap is inappropriate and leads to underestimation of the efficacy of test products.**

III. **Any final monograph for Topical, OTC healthcare antiseptic drug products should adopt methodology and performance criteria for the healthcare personnel handwash that correlate with the intended use and demonstrated antimicrobial efficacy of currently marketed alcohol-based hand antiseptic products that have been marketed for nearly two decades.**

INTRODUCTION:

The use of alcohol as an antiseptic agent can be dated back to the 2nd century AD. The first scientific studies of the *in vitro* properties of alcohol date back to the late 1800's, and alcohol was formally recommended for use as a skin antiseptic in the 1890's. Alcohol possesses rapid broad spectrum bactericidal activity and also demonstrates activity against many fungi and a variety of viruses (Ali, 2001). *In vivo* studies have demonstrated that 60% to 70% alcohol containing solutions reduce bacterial counts on the hands significantly better than washing hands with plain soap and water, and are as effective as or more effective than washing with antibacterial soap. Studies in both healthcare and non-

professional settings have proven the effectiveness of alcohol-based hand sanitizers at reducing disease (reviewed in Boyce, 2002; and SDA/CTFA, 2001). Furthermore, alcohol-based hand sanitizers provide exceptional timesaving in the healthcare system and encourage consistent, high frequency hand hygiene compliance resulting in further disease mitigation.

Based upon these scientific data and the safety profile of alcohol-based hand sanitizers, the use of alcohol-based hand sanitizers has been strongly recommended in multiple global standards including the "Guideline for Hand Hygiene in Health-Care Settings" (CDC Hand Hygiene Guideline) published jointly in 2002 by CDC, APIC, IDSA, SHEA and HICPAC (Boyce and Pittet, 2002). In the guideline, it was concluded that "alcohol-based handrubs 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."

I. Alcohol-based hand sanitizers have been proven to decrease disease transmission and increase hand-hygiene compliance in both healthcare and non-professional settings.

Hand disinfection is one of the most important measures for preventing hospital acquired (nosocomial) infections. Traditionally, compliance to hand hygiene has remained low due to the time constraints of washing with soap and water, poor sink accessibility, and dermatological intolerance. Alcohol-based hand sanitizers have proven to be an effective and accepted alternative to conventional handwashing practices in both healthcare and non-professional settings. A comprehensive summary of the scientific evidence has been presented to the FDA by the Soap and Detergent Association (SDA) and the Cosmetic, Toiletry, and Fragrance Association (CTFA) Industry Coalition in the form of a Citizen's Petition on August 6, 2001 (SDA/CTFA, 2001). Many

of these studies have also been discussed in the CDC Hand Hygiene Guideline (Boyce and Pittet, 2002). The examples presented below serve to highlight recent studies, which continue to demonstrate the importance of alcohol-based hand sanitizers in disease reduction.

Healthcare Settings:

- A 34 month study in an extended care facility compared the infection rates and infection types for units where an alcohol-based hand sanitizer was used to units where a control antimicrobial soap was used (Fendler et al., 2002). The overall infection rate decreased significantly (30.4%) during the study in the units using the alcohol sanitizer. The infection rates for the two most common infection types, urinary tract infections and respiratory infections, decreased by 18.2% and 21.9%, respectively.

- A second 69 month study at the same facility examined the efficacy of an alcohol-based hand sanitizer, a nearly identical alcohol-based hand sanitizer containing Triclosan, and a control antimicrobial soap (Hammond et al., in preparation, abstract attached). The overall infection rate in the units using alcohol sanitizer decreased by 34.4% (P=0.001) compared to units using the control soap. There were no statistical differences (P=0.26) between infection rates in units that used alcohol hand sanitizer and those that used alcohol hand sanitizer with Triclosan.

- A 16 month study examined the effect of the use of an alcohol-based hand sanitizer on infection rates and types in an orthopedic surgical unit of an acute care facility (Hilburn et al., 2003). Infection rates and types on the surgical unit for the period the alcohol-based hand sanitizer was used (10 months) were compared to infection rates and types for the same unit when the

alcohol-based hand sanitizer was not used (6 months). The results demonstrated a 36.1% decrease in infection rates for the 10 month period when the alcohol hand sanitizer was used.

- Trick et al. (2003) compared the efficacy of plain soap and water, an alcohol-based hand rub, and a medicated hand wipe (0.1% benzethonium chloride) against transient flora of surgical ICU nurses. Compared with use of plain soap and water, hand contamination with coagulase-negative staphylococci, *Candida* species, or any transient organism was less likely after use of an alcohol-based hand rub. In contrast, hands cleansed with the benzethonium chloride wipe were not statistically different from hands washed with plain soap and water.

Non-Professional Settings:

Several recent outcome studies have demonstrated the efficacy of alcohol-based hand sanitizers in non-professional settings (Hammond et al., 2000; Guinan et al., 2002; White et al., in press). These studies eloquently demonstrate that infection control is a continuum that extends beyond hospital walls and into the general community.

- In a study involving 16 schools in 5 individual school districts in 4 states, absenteeism due to illness was compared between schools using alcohol-based hand sanitizer and control schools (Hammond et al., 2000). Students and teachers in the product group used the hand sanitizer upon entering and leaving the classroom. Student absenteeism due to illness during the study was reduced by 19.76% in schools that used the alcohol-based hand sanitizer compared to the control schools ($P<0.05$). Additionally, data from the school system with the largest teacher population showed that teacher absenteeism decreased 10.1% (trend) in the schools where sanitizer was used.

- A second study examined the effectiveness of a comprehensive handwashing program on illness associated absenteeism in elementary schools (Guinan *et al.*, 2002). The study involved five (5) schools where each school had two control classrooms (no intervention) and two test classrooms (education program and hand sanitizer). Over a period of three months, the number of absences due to illness was 50.6% lower in the test classrooms ($P<0.001$) as compared to the control classrooms.

- White et al. (In Press) assessed the effectiveness of a hand hygiene campaign and the use of an alcohol gel sanitizer at decreasing the incidence of upper respiratory illness (URI) among students living in university residence halls. Four dormitories were paired into two control and two product groups where alcohol gel dispensers were installed in every room, bathroom and dining hall for the product groups. Data were collected for one semester and analyzed for statistical differences in reported symptoms, illness rates, and absenteeism from classes. The overall increase in hand hygiene behavior and reduction in symptoms, illness rates, and absenteeism between the product group and control group was statistically significant. Reductions in URI symptoms ranged from 14.8% to 39.9%, the total improvement in illness rate was 20.0% ($P<0.0001$), and the product group had 43% ($P<0.01$) fewer missed school/work days.

Compliance studies:

The overall effectiveness of HCPHW products is dependent not only upon antimicrobial efficacy but also upon compliance to hand hygiene practices. Traditionally, user compliance under study conditions rarely exceeds 40%. Healthcare workers have often cited time constraint as the main reason for non-compliance to handwashing regimens. In a critical study, Voss and Widmer

(1997) calculated time consumption for handwashing and alcohol hand disinfection (AHD) in a representative model intensive care unit. In order to achieve 100% compliance by conventional handwashing, 17% of the total work time would be consumed. In contrast, AHD from a bedside dispenser would consume less than 3% of the total work time. The authors concluded that achieving 100% compliance to handwashing would compromise healthcare, whereas achieving 100% compliance to AHD would not interfere with the quality of healthcare. The examples cited below further illustrate improvements in user compliance associated with alcohol-based hand sanitizer usage.

- An important study by Pittet et al. (2000) served to establish the link between hand hygiene compliance and infection prevention. Overall hand hygiene compliance was monitored before and during a hospital-wide hand hygiene campaign, which included emphasis on alcohol-based hand disinfection. Total nosocomial infection rates and occurrence of methicillin-resistant *Staphylococcus aureus* (MRSA) were monitored. Although recourse to handwashing with soap and water remained stable, frequency of hand disinfection substantially increased during the study period ($P<.001$). Overall nosocomial infection rates decreased from 16.9% in 1994 to 9.9% in 1998 and MRSA transmission rates decreased from 2.16 to 0.393 episodes per 10,000 patient days.

- In a similar study by Hugonnet et al. (2002), the effect of an intervention program, which included a hand hygiene poster campaign and distribution of individual bottles of an alcohol-based handrub, was assessed. Effectiveness was measured by observation of hand hygiene compliance through handwashing or handrubbing. Overall compliance increased from 38.4% to 54.5% during the study ($P<.001$). This overall increase was attributed to an increase in

handrubbing from 5.4% at baseline to 21.7% at the last survey (P<.001). In contrast, handwashing remained stable at around 30% across the surveys.

- Harbath et al. (2002) observed similar results from an intervention study performed in intensive care units at a pediatric referral hospital. Modest but statistically significant improvements in user compliance were noted after introduction of an alcohol-based hand gel as part of a quality improvement campaign. In contrast, compliance to handwashing and gloving remained stable for the duration of the study.

- Girard et al. (2001) demonstrated that introduction of an alcohol-based rub-in hand product into hospital units, coupled with user training improved both compliance of hand disinfection and skin condition of user's hands.

II. The healthcare personnel handwash test methodology and performance criteria proposed in the 1994 TFM are not appropriate to define the antimicrobial effectiveness of alcohol-based hand sanitizers.

The lack of correlation between the demonstrated health benefits of marketed HCPHW products and the 1994 TFM performance criteria for this category has been previously addressed in the SDA/CTFA industry coalition's August 2001 Citizen's Petition. We concur with the general principles/recommendations proposed in the 2001 Citizen's Petition and strongly encourage the FDA to adopt the coalition's recommendations. The current submission specifically addresses the inability of the 1994 TFM HCPHW method to appropriately predict the efficacy of alcohol-based hand sanitizers.

a. The HCPHW performance criteria do not reflect the antimicrobial efficacy of currently marketed products with clinically-proven effectiveness.

The *in vivo* test for effectiveness of a HCPHW described in the 1994 TFM (§330.470(b)(2)) is a modification of the American Society for Testing and Materials (ASTM) method ASTM E1174 (ASTM, 2001). The proposed performance criteria for the HCPHW in the 1994 TFM are a 2 $\log_{10}$ reduction in the test organism after the first wash and a 3 $\log_{10}$ reduction after the tenth wash (§333.470(b)(2)(iii), p.31448). These required reductions of the test organisms are inappropriate and do not reflect the performance of products known to reduce disease.

The SDA/CTFA joint committee conducted a review of published scientific literature and technical bulletins to examine the legitimacy of the performance criteria proposed in the 1994 TFM and have presented these data in the 2001 Citizen's Petition. Data were collected from 20 studies using alcohol-based hand sanitizer preparations containing ethanol at 60% to 70%. Of the 20 alcohol-based hand sanitizers tested, 17 (85%) met the required 2 $\log_{10}$ reduction after one wash. In contrast, only 2 of 18 (11.1%) met the required 3 $\log_{10}$ reduction after the tenth wash. Using criteria of a 1.5 $\log_{10}$ reduction in the marker organism after one wash (as recommended in the 2001 Citizen's Petition), 20 of 20 (100%) alcohol-based hand sanitizers would be acceptable.

Table 1 compiles HCPHW efficacy data from technical bulletins of a number of currently marketed alcohol-based hand sanitizers. The table illustrates that only four of ten products (40%) with available wash 10 data meet the 1994 TFM requirements for a 3 $\log_{10}$ reduction after the tenth wash. If the FDA were to adopt the performance criteria proposed in the 2001 citizen's petition (1.5 $\log_{10}$ reduction after one wash), eleven of eleven products (100%) would achieve the requirements. Alternatively, by simply eliminating the tenth wash

requirement ten of eleven products (91%) would meet the requirement for a 2 $\log_{10}$ reduction after the first wash.

TABLE 1: Comparison of marketed hand sanitizers against 1994 TFM and proposed HCPHW performance criteria.

Product	Alcohol	Additional Antimicrobial(s)	$\log_{10}$ Reduction		1994 TFM[1]	2001 Citizen Petition[2]
			Wash 1	Wash 10		
1	60% Ethanol	diazolidinyl urea, parabens, iodopropynyl butylcarbamate, phenoxyethanol, benzalkonium chloride	2.97	2.74	X	√
2	61% Ethanol	None	2.68	N.A.	N.A.	√
3	61% Ethanol	zinc pirithione, glyceryl laurate	3.43	3.10	√	√
4	62% Ethanol	None	2.84	1.91	X	√
5	62% Ethanol	None	3.83	2.86	X	√
6	62% Ethanol	None	2.59	1.97	X	√
7	62% Ethanol	None	3.93	2.15	X	√
8	62% Ethanol	None	3.93	3.74	√	√
9	62% Ethanol	Triclosan	3.36	2.57	X	√
11	62% Ethanol	diazolidinyl urea, parabens, iodopropynyl butylcarbamate	1.83	2.38	X	√
10	62% Ethanol	diazolidinyl urea, parabens, iodopropynyl butylcarbamate	3.16	3.28	√	√
12	80% Ethanol	None	3.98	3.22	√	√

[1] 2 $\log_{10}$ reduction after 1st wash, 3 $\log_{10}$ reduction after 10th wash

[2] 1.5 $\log_{10}$ reduction after 1st wash

√ - meets performance criteria, **X** - does not meet performance criteria, N.A. - No data available

Table 1 also lists ingredients with known antibacterial properties as identified on product ingredient disclosures. A correlation can be seen between the presence of additional antimicrobial ingredients and the ability of alcohol-based hand sanitizers to meet the wash 10 kill requirement. Of the four products meeting the FDA's wash 10 requirement, two have

supplemental antibacterial ingredients. Conversely, of the seven products that fail to meet the wash-ten requirement, only three contain supplemental antibacterial ingredients.

b. The efficacy of HCPHW products should be demonstrated after a single use. The demonstration of a cumulative effect following multiple applications should not be required.

Alcohol-based hand sanitizers are designed for routine, rapid hand disinfection and should be effective with each and every use, i.e., the first patient of the day should benefit as much as the last. It is inappropriate to require that the caregiver use the product repeatedly to obtain efficacy. Therefore, the most relevant sampling time for a hand sanitizer is after a single product usage, which is analogous to healthcare situations where personnel use the product immediately before and after interacting with a patient.

Historically, testing for cumulative (persistent) antimicrobial effect has been included in the HCPHW and Surgical Scrub categories, i.e., sampling after wash 10 or wash 11. However, this requirement for a cumulative effect is not appropriate for alcohol, which rapidly evaporates and does not show a cumulative effect in these tests. The FDA has acknowledged that alcohol is a non-substantive active ingredient and does not exhibit cumulative (persistent) effects (1994 TFM comments, p. 31412). Furthermore, alcohol has been designated an active ingredient in the antiseptic handwash or HCPHW category (§330.410(a)), and alcohol-based-hand sanitizers have been proven to be effective by a multitude of outcome studies (see key point I above). Therefore, cumulative antimicrobial effect has little relevance to the effectiveness of alcohol-based-hand sanitizers as defined by the ability to reduce disease transmission, and testing for it should not be required.

Nonetheless, the performance criteria for the HCPHW in the 1994 TFM force products to be formulated to achieve a cumulative (persistent) effect. To achieve this affect, alcohol containing products must to be supplemented with substantive (non-Category I) antimicrobial ingredients such as quaternary ammonium compounds, triclosan, and/or other preservatives (see Table 1). The technical bulletin from a product listed in Table 1 specifically comments: "[The product] uses 61% ethyl alcohol as the active ingredient combined with a preservative to produce a formulation that meets and exceeds the FDA's TFM testing as a healthcare personnel handwash". In fact, of the four products in Table 1 meeting the TFM performance criteria, only one product (Product 10) demonstrates increased efficacy at wash 10. This increase is modest (3.16 $\log_{10}$ reduction at wash 1 vs. 3.28 $\log_{10}$ reduction at wash 10) and likely not statistically significant.

Available data suggest the risk/benefit balance is insufficient to require a persistent effect for alcohol HCPHW's. There is no demonstrated clinical benefit to the incorporation of persistent antimicrobial ingredients into alcohol-based hand disinfectants designed for frequent, rapid hand hygiene (Larson, 2003). On the contrary, there are important potential downsides. Leave-on products pose much higher dermal exposure levels to the persistent biocides than traditional handwashes, have unknown long term effects upon natural skin flora, pose a potential 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.

c. **The efficacy of HCPHW products should be determined by comparison to the baseline survival of the marker organism. Comparison to a baseline wash performed with a non-**

antimicrobial soap is inappropriate and leads to underestimation of the efficacy of test products.

The 1994 TFM test methods for the HCPHW require that efficacy be measured by comparing survival of the test organism after product treatment to the baseline survival of the marker organism after washing with a "baseline control soap" (§333.470(b)(2)(iii)(H)(4), p.31449). This requirement does not reflect the actual usage pattern of HCPHW products; i.e., as an alternative to handwashing immediately before and after interacting with a patient.

The efficacy of the test product should instead be determined by comparison to the baseline survival of the marker organism as described in ASTM E1174. The ASTM standard method has never included washing with "baseline control soap", and there are no data to support this approach. Furthermore, the performance criteria proposed in the 1994 TFM were not derived from studies using baseline control soap. Conducting such a baseline control soap wash would likely make the proposed criteria for acceptance of a final formulation unachievable with almost any product that exists in the market today.

III. **Any final monograph for Topical, OTC healthcare antiseptic drug products should adopt methodology and performance criteria for the healthcare personnel handwash that correlate with the intended use and demonstrated antimicrobial efficacy of currently marketed alcohol-based hand antiseptic products that have been marketed for nearly two decades.**

The 1994 TFM has created a conflicting scenario for alcohol-based hand sanitizers designed for use as HCPHWs. Whereas FDA has recognized the safety and efficacy of 60-95% alcohol, establishing it as a Category I active ingredient, the test methods and performance criteria exclude the majority of alcohol-based hand sanitizer products. Furthermore, many of these products have

been established to reduce disease transmission. We urge FDA to consider several possible courses of action to correct this conflict to ensure that safe and effective alcohol-based hand sanitizers remain available without the need for extensive reformulation to include additional antimicrobial ingredients.

1. At a minimum FDA should eliminate the requirement for cumulative (persistent) effects from the HCPHW performance criteria. We strongly urge FDA to adopt the performance criteria for the HCPHW as recommended by the SDA/CTFA industry coalition in the August 6, 2001 Citizen's Petition (SDA/CFTA, 2001).

2. Alternatively, we recommend that FDA establish a separate product category for HCPHW products to be used without water (no rinse/waterless) and recognize 60% to 95% alcohol as a Category I ingredient. Currently, these products are classified as a subcategory under the antiseptic handwash or HCPHW category (§333.455(c)(2), p.31443). This alternative would be appropriate provided that FDA establish *in vivo* testing methods and performance criteria consistent with the well-known safety and efficacy profile of alcohol, including the lack of a cumulative (persistent) antimicrobial activity from alcohol.

Respectfully Submitted,

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Enclosures

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