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June 16, 2014

Ms. Leslie Kux
Assistant Commissioner for Policy
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-1975-N-0012, Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed amendment of the Tentative Final Monograph; Reopening of Administrative Record

Dear Ms. Kux:

The Society for Healthcare Epidemiology of America (SHEA) is pleased for the opportunity to provide input into the proposed rule. SHEA represents more than 2,000 physicians and other healthcare professionals globally with expertise in healthcare epidemiology and infection prevention. The Society promotes infection prevention by supporting science, research, guidelines, expert guidance, education, antimicrobial stewardship and transparency in public reporting related to healthcare associated infections (HAIs).

- 1) SHEA appreciates FDA's clarification in this proposed rule that, "We are not, at this time, proposing conditions under which OTC consumer antiseptic hand rubs (commonly called hand sanitizers) or antiseptics intended for use by health care professionals are Generally Recognized As Safe (GRAS)/Generally Recognized As Effective (GRAE)." Even so, **SHEA requests a careful measured approach relative to your deliberations involving regulatory actions for the antimicrobial ingredient, triclosan (TCS) [and very similar, triclocarban].**

SHEA Rationale/Comments: Healthcare personnel (HCP) are consumers too and often influenced by actions taken by the FDA. This influence also comes from family members, social connections and general purpose media. As such we are aware that HCP who work at affiliates of some of our members have been petitioned, either directly or indirectly, e.g. request of Supply Chain professionals, by their colleagues to remove use of TCS from their healthcare facilities. Limitations on the number of antimicrobials available for HCP will constrain provision of alternatives for situations where HCP develop irritant contact dermatitis to a particular antimicrobial agent.

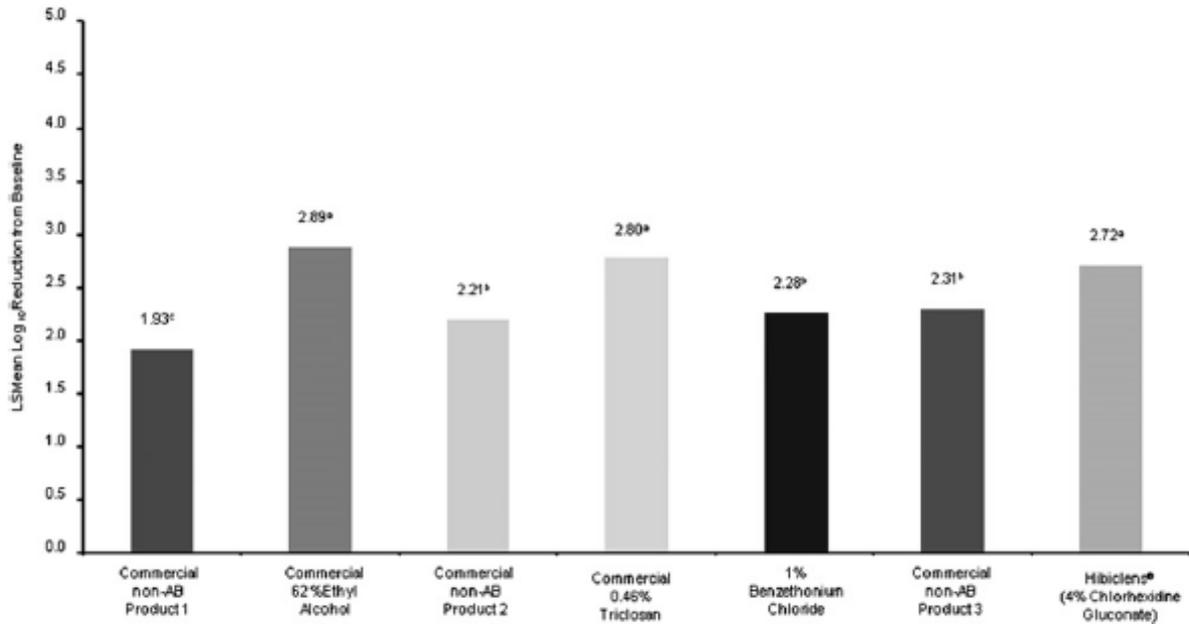
- 2) **SHEA agrees with the FDA's newly proposed amendment stating, "the record does not currently contain sufficient data to show that there is any additional benefit from the use of consumer antiseptic hand or body washes compared to non antibacterial soap and water."**

SHEA Comments: A landmark study by Luby, et. al. published in 2004 supports the FDA's conclusion – of note in an environment where there was substantial opportunity for exposure to microorganisms and where an antimicrobial soap could have demonstrated superiority.¹ In reflecting on comment 1) above, we do want to point out that there are studies involving use of TCS in healthcare facilities that do demonstrate efficacy.²⁻⁶ In addition we have attached an appendix that summarizes analysis of efficacy and other issues by the World Health Organization (WHO) in their 2009 Hand Hygiene Guideline that also find efficacy of this ingredient. Our long-range concern with actions involving TCS in your proposed Rule for OTC products for consumers may lead to unintended consequences by inhibiting availability of TCS for use in the health care industry. For example, TCS is used in institutional and industrial products, including dentifrice, fabrics, non-porous surfaces, and as a surface coating for certain medical devices such as antimicrobial sutures. Regarding the latter, there is a recent systematic review that finds these reduce incidence of surgical site infection (SSI).⁷ **SHEA has concerns with regard to what the response by manufacturers may be to any future actions by FDA to remove TCS from the marketplace for these other uses.**

- 3) **SHEA does support the need for ongoing studies to evaluate the safety and efficacy of antiseptics in consumer personal care products.** In particular we do support scrutiny of whether there is there an efficacy advantage to antimicrobial soaps over plain soap beyond what may be demonstrated in the laboratory under in vitro conditions. In addition SHEA agrees it is important to address the potential downside of widespread use of these products regardless of their efficacy. The potential risk to the environment, to society in the form of additional antimicrobial resistance pressure, and to the individual (e.g. how safe are the products in individuals given that issues of systemic absorption are raised in the background literature) need to be better understood in order to make a risk/benefit determination and for the public to make an informed decision along with approval for specific labeling/language from the FDA. We do recommend this risk assessment be as scientific as possible using best available methods as decisions built on theoretical concerns or solely on in vitro evidence are fraught with potential pitfalls such as disruption in availability of useful classes of antimicrobials.

4) **Prior FDA review:** SHEA does want to revisit a prior initiative by the FDA in 2005. The FDA did convene an expert Nonprescription Drug Advisory Committee (NDAC) “to review testing and efficacy data and to make recommendations for the approval of ingredients in consumer antibacterial hand washing products as over-the-counter drugs based on the criteria in their monograph for antiseptic healthcare.⁸ The NDAC proposed different test methods to assess efficacy of topical antimicrobials used by consumers and the overall efficacy testing results are provided below. In particular the authors concluded, “The antibacterial products, with the exception of the 1% benzethonium chloride prototype formula, yielded significantly greater log reductions than the non-antibacterial products (P <.0001). Although all treatments reduced bacterial counts, the formulations containing 62% ethyl alcohol, 0.46% triclosan, and 4% chlorhexidine gluconate were significantly better at reducing bacterial counts than all of the non-antibacterial products (P <.0001).” You do cite work of NDAC in your proposed rule but it’s not as evident that this component of NDAC’s work is reflected in the proposed rule.

SHEA Recommendation: We ask that the FDA revisit the work of the NDAC prior to enacting any new restrictions on TCS as the test data in the figure below indicate TCS might indeed be effective – even when used by consumers. We do not find citation of the NDAC’s investigation of alternative test methods led by Boyce et al. – in fact, the proposed rule fails to mention this efficacy data; albeit the alternative test method may not have as much relevance for use by consumers. Would you agree that the study by Boyce (see summary figure below providing log reduction results), using a proposed efficacy test method (palmar contamination) did find some efficacy that might be relevant to the health care sector?



source: Boyce JM et al 2012.

- 4) The proposed rule states, “Because of new concerns about the potential risks (e.g., resistance and hormonal effects) posed by the repeated daily use of consumer antiseptic washes (see section VII of this proposed rule), we are now proposing that a different type of effectiveness study is necessary to support the GRAE status of consumer antiseptic wash active ingredients. We are proposing that the use of antiseptic active ingredients to be used in consumer antiseptic wash products be supported by studies that demonstrate a direct clinical benefit (i.e., a reduction of infection). Data from these clinical outcome studies will help assure that any potential risk from consumer antiseptic wash products is balanced by a demonstrated clinical benefit.”

SHEA Comment: We understand this position; however this is dependent on the strength and quality of scientific evidence related to these new concerns being sufficient to warrant this higher threshold. For example, others such as Health Canada did not find excessive levels of TCS in waste water, evidence of bioaccumulation in humans nor clear indication TCS represents a significant threat to human health.⁹ Further, the evidence on promotion of cross resistance between use of TCS and antibiotics remains an in vitro phenomenon. Of note there is recent assessment of the possible connection between topical antimicrobial cleansing products and antibiotic resistance. More recent investigation of this in a select population of consumers did not identify selection for resistant strains of bacteria among skin flora of those who used TCS compared to those who did not as is also cited in your proposed rule.¹⁰ This type of applied research is helpful adjunct to in vitro studies.

- 5) **Clinical outcome studies: We agree available evidence to date does not clearly support efficacy or need for antimicrobial cleansing products by consumers.** The accumulated evidence to date however is modest and these are difficult studies to conduct. Even so we do support the FDA's examination of this scientific question.
- 6) **SHEA believes the following position of the Alliance for the Prudent Use of Antibiotics (APUA) strikes the appropriate balance on use of TCS:**

“When used in hospitals and other health care settings, or for persons with weakened immune systems, triclosan represents an important health care and sanitary tool. But outside of these settings, the American Medical Association has not endorsed the necessity or efficacy of triclosan and other antibacterial agents in personal care products, household products and commercial consumer products. According to the Centers for Disease Control and Prevention (CDC), vigorous hand washing in warm water with plain soap for at least 10 seconds is sufficient to fight germs in most cases, even for healthcare workers. For extra assurance, use of an alcohol- or peroxide-based hand sanitizer product is a good option. Triclosan has several important medical uses, and the future aim must be to retain these applications while eliminating the more frivolous and unnecessary ones. It would be

wise to restrict the use of triclosan to areas where it has been shown to be effective and most needed.”¹¹

- 7) **We have no additional, specific comments on the other antimicrobials addressed in the proposed rule, i.e. hexylresorcinol, Iodophor, Benzalkonium chloride, or chloroxylenol.** We tend to agree with your findings but do want to share that iodophor, chloroxylenol and chlorhexidine gluconate (not included in this proposed rule as it is approved under NDA) are frequently used in health care.

SHEA thanks the FDA for this opportunity to comment on the proposed rule regarding topical antimicrobials use by consumers. Overall we're supportive of this avenue of inquiry but we urge a careful, deliberate approach to assure unintended consequences are avoided.

Sincerely,

A handwritten signature in black ink, appearing to read "Daniel Diekema". The signature is fluid and cursive, with a small dot above the first letter 'D'.

Daniel Diekema, MD, FSHEA, FIDSA
President

References:

1. Luby SP, et al. Effect of intensive handwashing promotion on childhood diarrhea in high-risk communities in Pakistan: a randomized controlled trial. *JAMA*. 2004 Jun 2;291(21):2547-54.
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4. Jones RD, Jampani HB, Newman JL, Lee AS. Triclosan: a review of effectiveness and safety in health care settings. *Am J Infect Control*. 2000 Apr;28(2):184-96.
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6. Zafar AB, Butler RC, Reese DJ, Gaydos LA, Mennonona PA. Use of 0.3% triclosan (Bacti-Stat) to eradicate an outbreak of methicillin-resistant *Staphylococcus aureus* in a neonatal nursery. *Am J Infect Control*. 1995;23:200-8.
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8. Boyce JM, et al. An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial handwash products. *Am J Infect Control* 2012;40:742-9.
9. Second Report on Human Biomonitoring of Environmental Chemicals in Canada's HC Pub.: 130019 Cat.: H128-1/10-601-1E-PDF, ISBN: 978-1-100-22140-3.
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APPENDIX A

Excerpts from World Health Organization (WHO) Hand Hygiene Guideline, 2009;
Excerpts related to Triclosan (TCS)

For example, several investigators have found that health care-associated acquisition of MRSA was reduced when the antimicrobial soap used for hygienic hand antisepsis was changed.^{181,182} In one of these studies, endemic MRSA in a neonatal ICU was eliminated seven months after introduction of a new hand antiseptic agent (1% triclosan) while continuing all other infection control measures, including weekly active surveillance cultures.¹⁸¹ Another study reported an MRSA outbreak involving 22 infants in a neonatal unit.¹⁸² Despite intensive efforts, the outbreak could not be controlled until a new antiseptic agent was added (0.3% triclosan) while continuing all previous control measures, which included the use of gloves and gowns, cohorting, and surveillance cultures.

Concentrations ranging from 0.2% to 2% have antimicrobial activity. Triclosan has been incorporated in detergents (0.4% to 1%) and in alcohols (0.2% to 0.5%) used for hygienic and surgical hand antisepsis or preoperative skin disinfection; it is also used for antiseptic body baths to control MRSA. This agent is incorporated into some soaps (at a 1% w/v concentration) and a variety of other consumer products (deodorants, shampoos, lotions, etc.), as well as being integrated also into various dressings and bandages for release over time onto the skin. Triclosan enters bacterial cells and affects the cytoplasmic membrane and synthesis of RNA, fatty acids, and proteins.³⁹⁴ Recent studies suggest that this agent's antibacterial activity is attributable in large part to binding to the active site of enoylacyl carrier protein reductase.^{395,396}

A few reports suggest that providing HCWs with a triclosan-containing preparation for hand antisepsis has led to decreased infections caused by MRSA.^{181,182}

Laboratory studies involving exposure of some microorganisms to subinhibitory concentrations of triclosan have resulted in increased triclosan MICs. However, the clinical relevance of increased triclosan MICs generated in the laboratory is unclear, since affected strains remain susceptible to in-use concentrations of triclosan.^{401,402} Further research dealing with the relationship between triclosan use and antimicrobial resistance mechanisms is warranted, and surveillance for triclosan-resistant pathogens in clinical and environmental settings is needed.

Under laboratory conditions, bacteria with reduced susceptibility to triclosan carry cross-resistance to antibiotics.^{439,440} Reduced triclosan susceptibility or resistance was detected in clinical isolates of methicillin-resistant *S. epidermidis* and in MRSA, respectively.^{441,442} Of additional concern, exposing *Pseudomonas* strains containing the MexAB-OprM efflux system to triclosan may select for mutants that are resistant to multiple antibiotics, including fluoroquinolones.^{436,439,440} Nevertheless, a recent study failed to demonstrate a statistically significant association between elevated triclosan MICs and reduced antibiotic susceptibility among staphylococci and several species of Gram-negative bacteria.⁴⁴³ Clearly, further studies are necessary to determine if reduced susceptibility to antiseptic agents is of epidemiological importance, and whether or not resistance to antiseptics may influence the prevalence of antibiotic-resistant strains.⁴³³ Periodic surveillance may be needed to ensure that this situation has not changed.⁴⁴⁴

The frequency of skin irritation is concentration dependent, with products containing 4% most likely to cause dermatitis when used frequently for antiseptic handwashing.³⁴⁵ True allergic reactions to CHG are very uncommon (see also Part I, Section 14)

In general, irritant contact dermatitis is more commonly reported with iodophors.²²⁰ Other antiseptic agents that may cause irritant contact dermatitis, in order of decreasing frequency, include chlorhexidine, chloroxylenol, triclosan, and alcohol-based products. Skin that is damaged by repeated exposure to detergents may be more susceptible to irritation by all types of hand antiseptics formulations, including alcohol-based preparations.

Table I.11.7
Antimicrobial activity and summary of properties of antiseptics used in hand hygiene

Antiseptics	Gram-positive bacteria	Gram-negative bacteria	Viruses enveloped	Viruses non-enveloped	Mycobacteria	Fungi	Spores
Alcohols	+++	+++	+++	++	+++	+++	-
Chloroxylenol	+++	+	+	±	+	+	-
Chlorhexidine	+++	++	++	+	+	+	-
Hexachlorophene ^a	+++	+	?	?	+	+	-
Iodophors	+++	+++	++	++	++	++	± ^b
Triclosan ^a	+++	++	?	?	±	± ^a	-
Quaternary ammonium compounds ^c	++	+	+	?	±	±	-