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The Soap and Detergent Association and The Cosmetic, Toiletry, and Fragrance Association (SDA/CTFA Industry Coalition) provide these comments in advance of the March 23, 2005 meeting of the Nonprescription Drugs Advisory Committee. The SDA/CTFA Industry Coalition has submitted several detailed comments and has had extensive interchange with FDA in response to the June 17, 1994 Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products. During this time, the science surrounding topical antimicrobial skin antiseptics has continued to advance. The Coalition has been at the forefront of much of this evolution. While the basic perspective of the Coalition has not fundamentally changed since 1995, we believe our current position and recommendations, updated to include new information, data, and further validation of test methods outlined in the TFM, are very well-grounded in the latest science. We appreciate the opportunity to summarize our perspective and look forward to continuing dialog towards finalizing a monograph that establishes appropriate test methodology and performance criteria representative of a threshold of clinical effectiveness for this important category of healthcare drugs.

Critical Points

- Surrogate endpoint testing provides meaningful and appropriate tools to determine the threshold efficacy criteria for topical antimicrobial products

- The definitive, classical, prospective, randomized, and controlled clinical trials typically used to assess therapeutic benefit are not considered practical in measuring the prophylactic benefits of antimicrobial products

- Topical antimicrobial products approved under New Drug Applications (NDAs) may make additional claims and contain active ingredients not covered by the monograph. Different test methods, data analysis, and performance criteria may have been utilized, and may not be applicable to all monograph ingredients.

CTFA is the national trade association representing the cosmetic, toiletry and fragrance industry. Founded in 1894, CTFA has an active membership of approximately 300 companies that manufacture or distribute the vast majority of finished personal care products marketed in the United States. CTFA also includes approximately 300 associate member companies, including manufacturers of raw materials, trade and consumer magazines, and other related industries.

The Soap and Detergent Association is the non-profit trade association representing some 120 North American manufacturers of household, industrial and institutional cleaning products; their ingredients; and finished packaging. SDA members produce more than 90% of the cleaning products marketed in the U.S.

Discussion

Topical antimicrobial drug products are regulated either through a New Drug Application (NDA) or through the Monograph system. Their purpose and labeling are the same, *i.e.* to reduce the risk of infection by interrupting the transmission of pathogenic microorganisms. Consequently the test methodologies and the threshold of performance criteria that are used to assess effectiveness may be similar for both regulatory pathways, and ideally would be universally applicable to all active ingredients, and product forms. However, since products approved via NDAs may make additional claims, and may contain active ingredients not covered by the monograph, different test methods, data analysis, and performance criteria may have been utilized in their approval, and may not be applicable to current monograph ingredients.

A basic premise of the monograph system is that certain, well-defined categories of drug products that have been determined as safe and effective may be marketed without FDA pre-approval, as compared to the NDA system which requires that individual formulated drugs undergo separate review and approval. A key challenge for the monograph that addresses healthcare antiseptics is the determination and demonstration of efficacy for a category of drug products that encompasses several distinct active ingredients across a range of indications. In addition, the products covered by such a monograph largely provide a prophylactic benefit, rather than a therapeutic one. The definitive, classical, prospective, randomized, and controlled clinical trials typically used to assess therapeutic benefit are not considered practical in measuring prophylactic benefits of antimicrobial products (Larson, 1995).

Human clinical trials have a number of issues that can blur any potential efficacy result and can cause the size of the study to become so large that it is impractical or impossible to conduct. For example, the incidence of infection should be directly related to a specific dose of organisms that causes a particular infection. However numerous mitigating factors influence whether an infection can become established, including

immunological status of the host, route of infection, direct or indirect transfer of the infectious agent, etc. These factors make it difficult to calculate the level of bacterial reduction needed to demonstrate the benefit from the use of a primarily prophylactic agent. For these and other reasons, alternatives to classical, prospective, randomized, and controlled clinical trials must be used for topical antimicrobials.

Fortunately, there is a substantial body of scientific evidence that demonstrates the public health and clinical benefit of using topical antimicrobial products in healthcare settings. Such benefit has been demonstrated repeatedly through studies of bacterial transmission and infection rate reduction. These data allow for determination of a threshold of clinical effectiveness by benchmarking current antimicrobial products.

For purposes of a Monograph, it is necessary to establish efficacy methodology and criteria that insure a threshold of clinical effectiveness of topical antiseptics. Surrogate testing provides such a methodology. Such testing encompasses both *in vitro* and *in vivo* methodologies, and extensive comments have previously been submitted to the FDA on their validity.

The efficacy of topical antimicrobial products can be defined as the prevention or reduction of risk of bacterial transmission. The FDA in 1978 found that "the reduction of the normal flora, both transient and resident, has been sufficiently supported to be considered a benefit. The only determination that remains therefore, is how much of a reduction in microbial flora will be required to permit claims for the various product classes." (43 Fed. Reg. 1210). Thus, the Agency has previously embraced reduction of skin flora by a pre-specified amount as a valid surrogate endpoint for the efficacy of topical antimicrobial products in a clinical setting.

The SDA/CTFA Industry Coalition agrees that the use of surrogate endpoints to assess clinical effectiveness is a valid mechanism for ensuring that products meet a threshold of efficacy. Surrogate endpoint testing has been used in situations where there is a known benefit, and where standard validated methods have been developed that simulate product

use conditions, or where testing and proving a clinical claim would be impractical, or impossible. Such testing encompasses both *in-vitro* and *in vivo* methodologies, and extensive comments have been submitted previously to FDA on this subject.

With surrogate endpoints, it is possible to demonstrate a significant incremental benefit from the use of topical antimicrobial products. The SDA/CTFA Industry Coalition has previously submitted data on surrogate endpoints that represent a threshold of clinical effectiveness based on clinical and scientific literature. The surrogate endpoints that have been proposed were determined from controlled validated test methods that correlate to a threshold of effectiveness in the clinical environment.

Health Care Personnel Handwash

Health Care Personnel handwashes or waterless hand rub preparations are largely designed for the removal of transient microorganisms from the skin. These products are used in a clinical setting in an uncontrolled manner with little regard for the dosage (amount applied during hand washing), the exposure time, the repeat interval, or the amount of water used, if the product is intended to be used with water. Due to the nature of the product use, demonstration of efficacy in these products in an actual use setting would be, by definition, uncontrolled. Therefore, these products are tested in a controlled manner by validated methods that employ surrogate endpoints. An evaluation based on the elimination of a marker organism contaminating the hand such as *Serratia marcescens* or *Escherichia coli* is an appropriate way to measure effectiveness. Instead of relying on subject normal flora, these studies control the number of microorganisms on the hand by intentionally inoculating them with a known number of bacteria. In addition, these studies control the dosage, the exposure time to the antimicrobial and other factors. The results from these studies correlate well with literature reports for preparations containing effective ingredients such as 60% ethanol or 7.5% povidone iodine which show that a reduction of 1.2 – 2.5 $\log_{10}$ is achievable following a single application. The data supports the conclusion that a 1.5 log10 reduction is sufficient to demonstrate clinical benefit. The necessity for a demonstration of a cumulative effect for products

that are designed for multiple routine applications throughout the day has not been demonstrated clinically.

Surgical Scrub

Surgical scrub products are used by healthcare personnel immediately prior to donning sterile gloves for the performance of invasive procedures to reduce or eliminate transmission of microorganisms from their hands to the patient.

As with Health Care Personnel Handwash products, surrogate endpoints have been established for this clinical indication in deference to the impracticality of clinical trials to demonstrate reduction of patient infections. In this case, the rate of infection is thought to be very low so any clinical trial would be extremely large and difficult to control. A placebo control would be unethical in this situation so an active control would have to be employed, thus further decreasing the theoretical differences in infection rates between groups for the study and increasing the sample size. The low transmission rate has been confirmed in studies that have looked at this issue with mainly negative results. The coalition has previously presented information that supports microbial reductions of 1.0 $\log_{10}$ as accurately reflecting clinical efficacy as found from the scientific literature.

Pre-operative Skin Preparation

This clinical use is probably the most completely tested of the clinical indications contained in the TFM. It has long been considered unethical to even attempt a surgical procedure through intact skin without first cleansing the site, preferably with an antimicrobial formulation. Furthermore, attempts to prevent infection by administering systemic antibiotics prior to surgery demonstrated that topical antisepsis was superior.

Given the clinical evidence and the current standards of care at the time that the 1978 TFM was drafted, the Agency acknowledged the value of effective skin antisepsis prior to surgery and established surrogate endpoints. The coalition suggests that the groin performance criterion (3 $\log_{10}$) does not correlate well with clinical effectiveness, and in fact, may be unrealistic due to a low bacterial population at the skin site. The coalition

has previously presented information that supports microbial reduction of 2.0 $\log_{10}$ on the groin within 10 minutes of use as indicative of clinical benefit.

Preinjection Skin Preparation

One of the performance criteria addressed under Patient Preoperative Skin Preparation in the TFM is the Preinjection Skin Preparation performance criterion of a 1 $\log_{10}$ reduction of skin flora within 30 seconds of use. The coalition agrees that this is a suitable surrogate endpoint for clinical efficacy for this indication.

Clinical trials for this indication would be possible, but impractical. As with the previous indications, injection site infections are a rare occurrence and would require a multiple-day follow up period to assess the infection rate. Therefore, the surrogate endpoint for these studies is a reasonable alternative.

References

Bryce, EA, D. Spence, FJ Roberts. An in-use evaluation of an alcohol based pre-surgical hand disinfectant. Inf. Control and Hosp. Epid. 22;10: 635-639. 2001.

Doebbeling, B.N. G.L. Stanley, CT Sheetz, MA Pfaller, AK Houston, L Annis, N. Li, and R. Wenzel. Comparative efficacy of alternate hand-washing agents in reducing nosocomial infections in intensive care units. New England J. Med. 327:88-122. 1992.

Edwards PS, Lipp A., Holmes A. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Cochrane Review, The Cochrane Library 2004, Issue 3.

Ehrenkranz, NJ, BC Alfonso. Failure of bland soap handwash to prevent hand transfer of patient bacteria to urethral catheters. Inf. Control and Hosp. Epidemiology. 1991.

Jones, RD, J. Newman, and SY Hua. Antimicrobial hand gel as a primary means of hand disinfection: impact on selected nosocomial infections. Inf. Control and Hosp. Epid. 2000.

Kampf, G. and A. Kramer. Epidemiologic background of hand hygiene and evaluation of the most important agents for scrubs and rubs. Clinical Microbiology reviews 17,4: 863-893. 2004.

Larson, E. APIC Guideline for handwashing and hand antisepsis in health care settings. AJIC 23:251-269. 1995

Lucet, JC, MP Rigaud, F. Mentre, N. Kassis, C. Deblangy, A. Andremont, and E. Bouvet. Hand contamination before and after different hand hygiene techniques: a randomized clinical trial. J. Hosp. Infect. 50:276-280. 2002.

Maki, DG, M Ringer, and CJ Alvarado. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. The Lancet. 338: 339-343. 1991.

Sickbert-Bennett, E., Weber, D.J., M.F. Gergen-Teague, and W. Rutala. The effects of test variables on the efficacy of hand hygiene agents. Am. J. Infection Control 32,2:69-83. 2004.

Webster, J., JL Faoagali, and D. Cartwright. Elimination of methicillin resistant Staphylococcus aureus from a neonatal intensive care unit after handwashing with triclosan. J. Paediatr. Child health. 30:59-64. 1994.

Zafar AB, RC Butler. Results of handwashing in the control of a methicillin resistant Staphylococcus aureus outbreak. 1999.