

# CANTOX

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August 26, 2003

Documents Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, room 1061  
Rockville, MD 20852

**Re: Topical Antimicrobial Drug Products for Over-the-Counter Human Use;  
Health Care Antiseptic Drug Products; Reopening of the Administrative  
Record; Docket No. 75N-183H**

Dear Sir or Madam:

The following comments are submitted in response to the reopening of the administrative record, on May 29, 2003 (68 FR 32003), for the rulemaking for over-the-counter (OTC) topical antimicrobial drug products to, accept new comments and data concerning OTC health care antiseptic drug products. These comments are provided in support of a request for the inclusion of chlorhexidine gluconate (CHG) in the **Topical Antimicrobial Drug Products for Over-The-Counter Use; Health Care Antiseptic Drug Products** monograph as a Category I active antimicrobial ingredient at a range of 0.5% - 4.0%.

Pursuant to the Amended Tentative Final Monograph for Health Care Antiseptics, published in the Federal Register of June 17, 1994, CHG could only be marketed for professional or hospital use under an approved New Drug Application (NDA). At the time the Food and Drug Administration (FDA) considered CHG 4 % aqueous solution, used as a health care antiseptic, to be a new drug, on the basis of insufficient data to support general recognition of safety and effectiveness for OTC use. However, CHG has been marketed for a material time and a material extent to demonstrate its safety and efficacy for OTC use.

CHG is a bisbiguanide that achieves antimicrobial activity through disruption of cytoplasmic membranes. It is effective against Gram-positive bacteria, some Gram-negative bacteria, and viruses (Ekizoglu *et al.*, 2003; Spann *et al.*, 2003). CHG meets the criteria for an ideal topical antimicrobial in that it has a broad spectrum of activity with persistent antibacterial effects, and minimal toxicity or incidence of allergic effects.

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CHG was introduced to the United States *via* new drug approval procedures in 1997. CHG has since been the subject of at least 25 additional NDAs or abbreviated new drug applications (ANDAs), with concentrations ranging from 0.5 to 4.0%. A recent review of topical antimicrobial agents indicates that CHG is the antiseptic of choice as a presurgical prophylactic agent based on the results of several comparative investigations (Spann *et al.*, 2003). CHG's primary advantage is its prolonged germicidal activity, which persists for more than 6 hours after its initial application. In addition, CHG is minimally absorbed by the skin. The potential for skin irritation by CHG at concentrations below 4% is also low relative to other antiseptic products.

Although CHG was subject to marketing restrictions as a new drug in 1994, sufficient information is available supporting the safety and efficacy of CHG for OTC use. In addition to its pharmaceutical advantage over other OTC antiseptic agents (due to its prolonged germicidal activity), its wide margin of safety makes CHG an excellent choice for inclusion as a Category I ingredient in the monograph for health care antiseptics. This is supported by years of marketing data, both in drugs sold as prescription products in the United States, as well as from available foreign marketing data. CHG is currently present as the active ingredient at levels ranging from 0.5 to 4% in at least 12 different OTC topical solutions approved by the FDA, and CHG is also present in a number of FDA-approved OTC dental solutions and topical sponges. In addition, CHG is listed in the *British Pharmacopoeia* and *British National Formulary* and is recognized as safe and effective as an active ingredient in OTC antiseptic drug products worldwide. In Canada, CHG is subject of an OTC *Category IV Monograph* for antiseptic skin cleansers at concentrations of 2.0 – 4.0%, with at least 30 OTC drug products with this active ingredient. CHG is on the World Health Organisation (WHO) *Model List of Essential Medicines* because it is considered to be an efficacious, safe, and cost-effective antiseptic for priority conditions in a basic healthcare system (WHO, 2002). These products have been marketed for a significant time and extent (*i.e.*, continuously in countries world-wide, including the US, for over 5 years).

Further, based on a comprehensive review of the scientific literature published on the safety and effectiveness of CHG as a topical antimicrobial since 1994, recent clinical and *in vitro* data indicate that CHG, at levels up to 4%, is an effective antimicrobial agent when used topically (APIC, 1995; Faoagali *et al.*, 1995; FDA, 1999; Spann *et al.*, 2003; Ekizoglu *et al.* 2003; Weber *et al.*, 2003).

Adverse event reports associated with CHG use have been limited to hypersensitivity reactions associated with CHG in medical devices, and these cases were not related to its use as a topical antiseptic handwash. (It should be noted that many of the reports were not new cases and have already been considered in previous assessments.) The Cosmetic Ingredient Review (CIR) Panel has evaluated these reports and continues to support its previous conclusion that CHG is safe for use in cosmetic products at concentrations up to 0.2% (CIR, 1999). The use of antiseptic handwash products containing CHG at levels up to 4% is not expected to result in a significant increase in the incidence of hypersensitivity reactions, based on the long history of use of such products.

CHG-based products provide a safe and effective option to be included in an antiseptic handwashing regimen for healthcare workers. If these products are included as part of such a program along with other hand cleansers, such as soap, alcohol-based rinse-free cleansers, and other antimicrobial-based products (*i.e.*, rotate CHG products with other antiseptic products), this could help to 1) reduce the incidence of skin irritation from repeated use of a single product or products with the same active ingredient, and 2) decrease the rate of possible microbial resistance by providing a safe and effective alternative. The availability of CHG-based products could also encourage compliance with handwashing procedures by providing workers with more options. As compliance with handwashing procedures has been shown to be lacking among health care workers (Bischoff *et al.*, 2000), any efforts to increase this activity should be considered, including the provision of a number of handwashing options such as a variety of antimicrobial products (including CHG-based products), alcohol-based rinse-free cleansers, and soaps. This way, health care workers could choose from a selection of safe and effective products for their hand hygiene practices.

CHG is considered both pharmacologically safe and effective for use as an antiseptic drug product, and world-wide consumer use of CHG in OTC products for many years has demonstrated that it can be used safely and effectively as an antiseptic skin cleanser in an OTC environment. It is therefore our position that CHG has been marketed for a material time and extent and been shown to be a safe and efficacious ideal active ingredient for inclusion in the **Topical Antimicrobial Drug Products for Over-The-Counter Use; Health Care Antiseptic Drug Products** monograph as a Category I ingredient.

Sincerely,



Earle Nestmann, Ph.D.  
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