



Consumer Healthcare  
Products Association



October 27, 2005

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

Re: Docket No. 2005D-0240: Draft Guidance for Industry on Gingivitis:  
Development and Evaluation of Drugs for Treatment or Prevention; Availability  
70 Fed. Reg. 37102-37103 (June 28, 2005)

Dear Sir or Madam:

The following comments are submitted by the Joint Oral Care Task Group (the Task Group) of the Consumer Healthcare Products Association (CHPA)<sup>1</sup> and the Cosmetic, Toiletry, and Fragrance Association (CTFA)<sup>2</sup> with respect to the Draft Guidance for Industry on Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention.

The two trade associations formed the Task Group to address regulatory issues affecting oral care products that their member companies develop, manufacture, and distribute.<sup>3</sup> The Task Group members manufacture and distribute a wide variety of products, including dentifrices and mouthwashes. The Task Group has welcomed the opportunity to be a participant in the rulemaking process for OTC antigingivitis drug products and appreciates the opportunity to comment on the proposed industry guidance on gingivitis.

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<sup>1</sup> CHPA, founded in 1881, is the national trade association representing manufacturers and distributors of OTC drugs and nutritional supplements. CHPA members account for more than 90 percent of retail sales of OTC drugs in the United States.

<sup>2</sup> Based in Washington, D.C., CTFA is the trade association representing the cosmetic, toiletry, and fragrance industry in the United States and globally. Founded in 1894, CTFA has a membership of nearly 600 companies, including manufacturers, distributors, and suppliers for the vast majority of finished personal care products marketed in the United States.

<sup>3</sup> The Task Group members are Access Business Group; Church & Dwight Co., Inc.; Colgate-Palmolive Company; GlaxoSmithKline; Pfizer Inc; and The Procter & Gamble Company. These comments represent a consensus developed among the Task Group's membership, but do not supersede or preclude comments by individual members.

We support FDA's development of a guidance to aid drug sponsors in designing and conducting clinical trials either to submit additional information to the antigingivitis rulemaking (advance notice of proposed rulemaking (ANPR) for antigingivitis/antiplaque drug products) or to obtain approval for a new antigingivitis drug through the NDA process.

Comments on specific referenced sections of the draft guidance are as follows:

### **III. General Considerations**

#### **B. Prevention vs. Treatment Claims**

As stated in the Task Group's November 25, 2003 comments on the ANPR for antigingivitis/antiplaque drug products, the indications and uses for OTC antigingivitis drug products should be broadened to allow multiple descriptions for the drug effect on gingivitis. The Task Group proposed that one or more of the words "control," "reduce," and "prevent" may be used to describe the action of the antigingivitis agent on gingivitis. This is because consumers, purchasing an OTC antigingivitis product, may use it to control, reduce, and/or prevent gingivitis. The Task Group, therefore, recommends the draft guidance indicate that each of the above-named actions – controls, reduces, and/or prevents gingivitis – is an appropriate OTC claim, and that more than one of the claims can be made by an OTC product.

#### **C. Mechanism of Action**

This section should be reworded to clarify that plaque control can represent not only a reduction in the plaque mass but also a reduction in the pathogenicity, and indications/claims should be commensurate with antiplaque effects. For further explanation, please see Task Group's November 25, 2003 comments on the ANPR for antigingivitis/antiplaque drug products, Section 7: Mechanisms Other than Plaque Mass Reduction that Produce an Antigingivitis Effect.

#### **E. Combination Products**

The Task Group recommends that the wording in this section be simplified to the following:

“Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects. Therefore, to demonstrate the contribution of each component, the combination product must be shown to have a greater effect than either one separately, which can be tested by including each component as a separate treatment adjunct to SRP.” (Hyman et al., 1997)

Given the clarity of the above statement, we do not believe an example, such as the one provided in the draft guidance, is helpful or necessary.

F. Ethical Considerations of Conducting a Gingivitis Trial

The Task Group agrees with FDA that subjects should not be exposed to permanent detrimental health outcomes as a result of participation in a gingivitis clinical trial. We question, however, the Agency's general position that use of experimental gingivitis models, which accelerate the development of gingivitis, may raise ethical concerns and were only used "in the past." Experimental gingivitis models are used today to provide valuable information in screening potential therapeutic agents for their effect on plaque-induced gingivitis. The ANPR for antigingivitis/antiplaque drug products includes an experimental gingivitis model as a final formulation performance test for products containing the fixed combination of essential oils. Experimental gingivitis models are generally of two to three weeks' duration, which is a short enough period of time that it should not raise a concern for the health of subjects. Institutional Review Boards are familiar with these short-term experimental gingivitis models and agree with the appropriateness of the risk for subjects. Therefore, the Task Group recommends the Agency adopt the general position that short-term experimental gingivitis models (two to three weeks' duration) do not raise ethical issues and that short-term experimental gingivitis models are valuable in the early phase of drug development and for performance testing for some products. For these reasons, we request the Agency remove the last paragraph in this section.

V. **Clinical Protocol Issues and Elements**

A. Study Design

The Task Group agrees with the recommendation of the Agency that a split-mouth design should not be used, because it is very difficult to segregate the test agent to only one side of the mouth. The Task Group supports use of: (1) parallel treatment groups, or (2) cross-over designs where there is a sufficient wash-out period to eliminate any residual effects of the prior treatment.

B. Randomization

The Task Group recommends the Agency establish the purpose and principles of randomization at the beginning of this section. We suggest the Agency consider using the principles in the ICH Statistical Principles for Clinical Trial document (Section 2.3.2. Randomization) that states that the purpose of randomization is "to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments" and to provide a "sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects." Thus, a drug product's effect on gingivitis should not be affected by parameters other than the active ingredient(s) itself. We generally agree with the Agency's comment that "In the case of an important potential confounder, such as baseline gingivitis or smoking, it may be prudent to stratify the groups by this factor before randomization. In some cases, adjustments for baseline characteristics may be accomplished statistically after

the trial, to correct for differences.” However, we recommend that the phrase “such as baseline gingivitis or smoking,” which was included in the original statement by FDA, be removed because this wording suggests that these factors, and only these factors, should be considered in a study design. Additionally, the first sentence in the second paragraph, which states that “age, gender, and disease severity are important factors in considering the adequacy of randomization,” can be deleted because this subject is adequately covered in the balance of this section.

### C. Blinding

The Task Group agrees that a “double-blinded” trial is the “gold standard.” However, as mentioned in subsections “F. Placebo or Active Control Formulation” and “G. Use of a No-treatment Group” of this section, it may not always be possible to achieve the double-blind ideal. This is especially true in a clinical study that may include a no-treatment group and/or a positive control group. Because the positive control may be a currently marketed product that cannot be blinded, differences between the test and positive control products may be discernable. Additionally, when a no-treatment arm is used, subjects will not receive a product and would be instructed to maintain their normal home oral hygiene practices, which would make evident that they were not using a test product. In discussing these cases, the Task Group suggests the Agency follow the guidance of the ICH Statistical Principles for Clinical Trials (Section 2.3.1 Blinding). For example, this section states that if a double-blind trial is not feasible, every effort should be made to minimize the various known sources of bias and that “clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment.” The ICH guidance also states that “the reasons for the degree of blinding adopted should be explained in the protocol, together with the steps taken to minimize bias by other means.” Because the use of an active control or no-treatment group can impact blinding, we recommend that subsections F and G be combined and discussed in this section.

### E. Standard of Care

The standard of care advocated in this section calls for regular brushing and the “use of dental floss between professional dental visits to maintain oral health and reduce the incidence and severity of gingivitis.” The requirement of daily flossing is not consistent with the habits and practices of the general population. The Task Group recommends that, for OTC drug products, regular brushing and continuation of their other current mechanical oral hygiene practices, whether or not this includes flossing, be used in clinical studies. Regular brushing and use of current mechanical oral hygiene practices will provide a better indication of the product’s efficacy in a general OTC population.

### F and G. Placebo or Active Control Formulations/Use of a No-treatment Group

We support moving these two sections under section V. C. “Blinding.”

## **VI. Considerations for Subject Recruitment**

### **B. Inclusion and Exclusion Criteria**

The draft guidance recommends that “a product intended to be marketed OTC be studied in a population which includes a full range of gingivitis within the indication for nonprescription users to reflect the population that will ultimately use the product.” The Task Group does not believe the Agency intends to study gingivitis in a population that does not have the disease and therefore recommends that the last sentence of the first paragraph be modified as follows:

“We recommend that a product intended to be marketed OTC be studied in a representative OTC gingivitis population, but not in a population that does not have gingivitis.”

### **C. Special Populations**

The Task Group agrees that clinical efficacy studies should examine the effects of gender, age, and race. However, the Task Group does not believe that gender, age, and race necessarily constitute a “special population,” because these demographics are already incorporated into adequate clinical designs. We do support the conduct of a study in a special population, if needed, to investigate an outcome for a specific population that has been identified in one of the exploratory or pivotal clinical efficacy trials.

### **E. Geriatric Populations**

We are not aware of any data that suggest that geriatric subjects may respond differently to OTC antigingivitis agents compared to the general OTC consumer population or younger adults. Therefore, we support removal of this section or limiting its reference to prescription drug products.

## **VII. Assessment of Gingivitis**

### **B. Gingival Index**

This section also appears to limit the number of indices that can be used to measure gingivitis. The Task Group believes that this guidance should not be prescriptive or restrict the methodologies used, but rather be inclusive of any valid and robust gingivitis index. In addition, the draft guidance should encourage investigators to investigate new indices that provide meaningful and clinically relevant measures of gingivitis and to provide validation supporting the use of these newer indices.

The draft guidance states that the Loe and Silness Gingival Index is “widely used today.” Actually, the two most commonly used gingival indices are modifications of

the Loe and Silness Gingival Index, namely the Mandel-Chilton Gingival Index (Talbot et al., 1977) and the Modified Gingival Index (Lobene et al., 1986).

The draft guidance also indicates that “the scores from the four gingival units are averaged to obtain a score for each tooth, and these scores are combined and averaged to determine a score for the individual.” The number of gingival units should not be specified, as this is applicable to the Loe and Silness Gingival Index but may not be applicable to modifications. For example, the Mandel-Chilton Gingival Index scores six units per tooth. Current industry practice is not to average scores for each tooth before developing an average for the individual’s mouth, but rather to sum scores over the subject’s entire mouth and divide by the number of gingival units.

The last sentence in this section does not appear to belong and should be removed.

#### C. Plaque Index

The Agency’s statement about its current thinking that “antigingivitis drugs using a mechanism other than plaque reduction, such as anti-inflammation, could be approved as prescription drugs,” implies that such drugs cannot be approved as an OTC drug product. The Task Group believes that this may be interpreted too narrowly and that, under the right circumstances, an anti-inflammatory drug might be approvable as an OTC drug product.

#### D. Bleeding on Probing

The Task Group recommends that the first sentence in this section refer to bleeding and not to “bleeding on probing” as a cardinal sign of gingivitis. This is because consumers may notice bleeding alone which would prompt them to see their dentist and/or use an OTC antigingivitis drug product. The majority of the Task Group recommends that the last sentence in this section be modified to reflect that bleeding could be a stand-alone primary outcome, if this measurement is shown to be validated and appropriate thresholds are established.<sup>4</sup>

#### E and F. Calculus Formation/Staining Index

The Task Group believes that inclusion of a section on calculus formation and staining index between the sections on bleeding and microbiological sampling is confusing because both calculus formation and staining are cosmetic outcomes. These two cosmetic outcomes are usually evaluated during the course of the development of the product and should not necessarily be required to be evaluated in the pivotal clinical efficacy trials. Because both calculus formation and staining are not primary outcomes of a clinical trial evaluating gingivitis, the Task Group

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<sup>4</sup> Pfizer Inc holds a minority position on bleeding as a stand-alone primary outcome and will submit under separate cover its comments on this issue.

recommends inclusion of these two outcomes in a separate section at the end, entitled “Other Measurements.”

#### G. Microbiological Sampling

This section should be moved to Safety Considerations (Section IX). Because specific microorganisms in plaque or in the mouth cannot be used as a surrogate for the treatment or prevention of gingivitis, sampling the microbiological flora in the mouth serves to identify any significant shifts in flora. Hence, microbiological sampling provides an important safety parameter and not an assessment of gingivitis.

### **VIII. Clinical and Statistical Significance for Determining an Effect**

#### B. Statistical Considerations

In the third paragraph of this section, bleeding is described as a “site-specific dichotomous variable” where “a repeated measures approach may be appropriate.” Current standard industry practice and gingival clinical literature summarizes the bleeding site data on a per-subject basis, either by the total number of bleeding sites in the mouth, by the proportion of sites with bleeding (of the total sites examined in the mouth), or by the use of a gingival bleeding index. These variables are then subjected to analysis of covariance methodology in a similar fashion as are the GI and plaque index (PI), with possible mathematical transformations applied. We believe that this standard practice should be included in the guidelines regarding the analysis of bleeding data.

### **IX. Safety Considerations**

The Task Group agrees that, in some consumers, periodontitis may co-exist with gingivitis. Ingredients that have their effect through mechanisms other than plaque control, should address the question of masking of periodontitis.

The last paragraph in this section suggests that both staining and calculus are safety considerations. Because both staining and calculus are cosmetic endpoints, the Task Group recommends that they be included in a section entitled: “Other Measurements,” rather than under “Safety Considerations.”

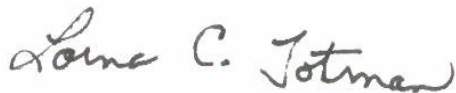
### **X. Concluding Comments**

The guidance indicates that requests for meetings and requests for procedural clarification should be directed to the Supervisory Project Manager in the Division of Dermatologic and Dental Drug Products. With the formation of the Office of

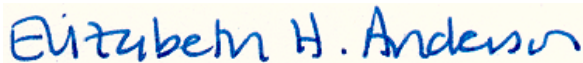
Nonprescription Products, we encourage the Agency to give this new office primary responsibility for direct OTC NDAs and Rx-to-OTC switch NDAs for potential OTC antingivitis drug products.

In summary, the Task Group supports the development of an industry guidance for gingivitis. If the Task Group can provide any clarification of its comments or provide any further assistance, please contact the undersigned.

Submitted on behalf of the CHPA/CTFA Joint Oral Care Task Group,



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