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

RE: Docket No. 81N-033P – Oral Health Care Drug Products for Over-the-Counter Human Use; Antigingivitis/Antiplaque Drug Products; Establishment of a Monograph: Proposed Rules (68 Fed. Reg. No. 103, Page 32232, May 29, 2003)

This document is being submitted by Colgate-Palmolive Company (Colgate-Palmolive) in reply to certain comments submitted to FDA by industry in response to the May 29, 2003 publication of the aforementioned proposed rulemaking. In this proposed rulemaking, the Food and Drug Administration (FDA) requested information and comments to the Docket based on the Agency's intention to establish conditions under which over-the-counter (OTC) drug products for the reduction or prevention of dental plaque and gingivitis are generally recognized as safe and effective and not misbranded.

Final Formulation Testing Requirements for Stannous Fluoride Products

Industry Comment:

On November 21, 2003 Procter & Gamble submitted comment recommending that the Plaque Glycolysis and Regrowth Model (PGRM) should be the only performance test required for marketing stannous fluoride dentifrice.

Procter & Gamble proposed this in the context of its additional recommendation that a stannous fluoride dentifrice should be allowed to bear a labeling statement relating to plaque control and/or plaque reduction.

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Two primary arguments have been put forward to support this recommendation:

1. Recent clinical studies¹, using improved measures of plaque accumulation, have revealed significant efficacy for stannous fluoride in reducing plaque mass in a clinical setting
2. Stannous fluoride provides its anti-gingivitis effects through modulating plaque metabolic processes.

Colgate-Palmolive's Response:

Colgate-Palmolive does not support the above recommendation on performance testing. While measurement of plaque metabolism via PGRM is relevant to bioequivalence of products bearing plaque interference labeling statements, it is insufficient to establish bioequivalence of a final formulation to a clinically tested stannous fluoride standard in respect of a labeling statement relating to plaque control and/or plaque reduction.

Colgate-Palmolive proposes that the primary test of the final formulation efficacy to support a labeling statement of plaque control and/or plaque reduction should be a short term *in vivo* measure of plaque accumulation. Specifically, a comparison of the effects of a final formulation to the clinically tested stannous fluoride standard on *in vivo* plaque accumulation would establish bioequivalence in respect of plaque mass reduction.

Colgate-Palmolive suggests that the most relevant short term *in vivo* test is the Experimental Gingivitis (EG) model. This model was proposed by the Warner Lambert Company (now Pfizer) because it has been well established as a predictor of plaque and gingivitis efficacy in 6 month brushing studies. On this basis, it was accepted by the Dental Plaque Subcommittee as the primary test to establish performance of a final formulation containing the essential oils, thereby supporting labeling statements of plaque control and/or plaque reduction, as well as gingivitis control and/or gingivitis reduction.

In an effort to support the recommendation that a stannous fluoride dentifrice be allowed to bear a labeling statement relating to plaque control and/or plaque reduction, Procter & Gamble submitted the results of plaque assessments made during a short term Experimental Gingivitis (EG) evaluation. An important point in their argument was the observation that the efficacy of the stannous fluoride standard compared to a control in reducing dental plaque accumulation was

¹ Page 63 of Procter & Gamble Company's Comments in response to the Advance Notice of Proposed Rulemaking on OTC Antigingivitis/Antiplaque Drug Products (November 21, 2003).

significantly higher in the Experimental Gingivitis model (19%) than in their previously cited conventional 6 month brushing study (6.9%). This result is consistent with independent, published studies. The result may be explained by the confounding effects of brushing in the 6 month study; there is no brushing to confound the chemical effects of stannous in the EG model. In additional support of their recommendation regarding plaque reduction, Procter & Gamble submitted data utilizing a highly sensitive state-of-the-art imaging technique (DPIARM) to demonstrate significant and reproducible efficacy for stannous fluoride compared to control in reducing plaque accumulation *in vivo* (11.5% - 34.9% in six studies). Together, the new data submitted by Procter & Gamble fully support the sensitivity and predictability of the Experimental Gingivitis model, and specifically validates this model for final formulation testing of stannous fluoride dentifrice.

A second element of our argument is that this test, (PGRM) is insufficient on its own to establish bioequivalence of a final formulation to a clinically tested stannous fluoride standard in respect of a labeling statement relating to plaque control and/or plaque reduction pertains to the precise nature of the PGRM test.

In their comments, Procter & Gamble pointed out that the localized action of dental plaque is important in promoting the host response and in the resultant cascade of sequelae associated with gingivitis. Procter & Gamble specifically discussed the large body of research pertaining to the pathogenicity of plaque associated with gingivitis. They cite microbial species in plaque and variable metabolic products of plaque including ammonia, lipopolysaccharides, short chain fatty acids and a variety of lytic enzymes as the key virulence factors in the development of gingivitis. Colgate-Palmolive concurs with this summary. Furthermore, we would like to point out that these metabolic products are derived from pathways that are specific to the periodontal pathogens, such as *Porphyromonas gingivalis*, *Prevotella intermedia* and *Fusobacterium nucleatum*, and to the virulence factors of gingivitis and early periodontal disease.

Importantly, Procter & Gamble did not suggest that plaque glycolysis is a virulence factor in gingivitis per se. However, they propose that plaque glycolysis is a measure of plaque metabolic activity which is relevant to gingivitis. Colgate-Palmolive recognizes that plaque glycolysis is a simple measure of plaque metabolic activity. However, we do not agree that plaque glycolysis is a relevant measure of any of the key metabolic processes that are important in the development of gingivitis. In contrast, we point out that plaque glycolysis is the key metabolic process involved in the development of caries. Specifically, it is the metabolic pathway responsible for plaque acid generation by the two caries pathogens, *Streptococcus mutans* and *Lactobacillus casei*, and these are the key virulence factors in the caries process.

In summary, Colgate-Palmolive disagrees with Procter & Gamble's proposal that the Plaque Glycolysis and Regrowth Model is an appropriate surrogate measure of the clinical efficacy of a final formulation of stannous fluoride dentifrice labeled for plaque control and/or plaque reduction.

Colgate-Palmolive suggests that the Experimental Gingivitis model is a particularly appropriate measure of the clinical efficacy of a final formulation of stannous fluoride dentifrice bearing a labeling statement relating to plaque control and/or plaque reduction, as well as to gingivitis control and/or gingivitis reduction.

Use of the Experimental Gingivitis method would align the final formula testing of stannous fluoride and the essential oils

Final Formulation Testing Requirements for Cetyl Pyridinium Chloride Products

Industry Comment:

In their November 21, 2003 comment, Procter & Gamble also recommended that the Disk Retention Assay and the Plaque Glycolysis and Regrowth Model (PGRM) should be the performance tests required for marketing Cetyl Pyridinium Chloride rinses.

Colgate-Palmolive's Response:

During the comment period, significant discussion took place between oral care product manufacturers, the CHPA and the CTFA regarding the value of proposing a guidance approach to both clinical efficacy testing and final formulation testing. In this context, Colgate-Palmolive respectfully suggests that a uniform approach to final formulation testing would be rationale, desirable and appropriate.

Colgate-Palmolive suggests that the Experimental Gingivitis model is an appropriate measure of the clinical efficacy of a final formulation of cetyl pyridinium chloride bearing a labeling statement relating to plaque control and/or plaque reduction, as well as to gingivitis control and/or gingivitis reduction.

Use of the Experimental Gingivitis method for cetyl pyridinium chloride would align the final formula testing to that proposed for stannous fluoride and endorsed for the essential oils. Furthermore, it would provide a framework for (or guidance approach to) final formulation testing of newly designated Category I actives in the future.

Additional Ingredients Acceptance to the Monograph

Industry Comment:

On November 19, 2003 the Ciba Specialty Chemicals Corporation submitted comments requesting that the ingredient "Triclosan" be accepted as Category I or III based on established public information.

Colgate-Palmolive's Response:

Colgate-Palmolive does not support Ciba's comments. We do not believe they have provided adequate data to support their request for Category I status.

Recommendations for Revised Warning Statement

Industry Comment:

Also contained in Procter & Gamble's November 21, 2003 submission was the statement: "It is our position that the warnings specified in this rulemaking for all Category I active ingredients are inappropriate and are inconsistent with labeling for an NDA-approved gingivitis product."

Colgate-Palmolive's Response:

As the Agency and our industry colleagues are aware, Colgate-Palmolive Company is the sponsor for NDA 20-231 for Colgate Total, the referenced NDA product. Colgate-Palmolive believes that reference to Colgate Total is inappropriate since as a NDA product, it underwent a different review process, which supports its current labeling. Hence, we strongly feel that Colgate Total should not be used as a support mechanism for approval of the modified Warning statements.

Should you have any questions regarding these comments, please do not hesitate to contact me.

Respectfully submitted,



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