



**Volume II**

## WhiteHill Oral Technologies, Inc.

*Ira D. Hill, PhD*  
9200 Prince William  
Austin, TX 78730

512-241-0533 voice  
512-241-0534 fax  
irahill@sbcglobal.net

*Robert D. White*  
435 Orangeburg St. SE  
Aiken, SC 29801

803-642-8037 voice  
803-642-8038 fax  
mfilippone@verizon.net

July 26, 2005

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, Maryland 20852

Re: Docket No. 2005D-0240  
Draft Guidance for Industry  
“Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention”  
Published in the Federal Register June 28, 2005  
Volume 70 Number 123, pp 37102-37103  
Comment: Reduction and Prevention of Oral Health Problems Claim in  
OTC Oral Antiplaque Drug Products

WhiteHill Oral Technologies, Inc., submits these comments in response to the publication by FDA of the Draft Guidance for Industry, “Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention” published in the Federal Register, June 28, 2005, Vol. 70 Number 123, pp. 38102-37103. WhiteHill manufactures products intended for use in the oral cavity, some marketed for cosmetic purposes and others for drug purposes. Representatives of WhiteHill participated extensively during the public hearings conducted by the Plaque Subcommittee.

In response to the proposed Guidance for Industry, which “focuses on plaque-induced gingivitis”, WhiteHill is submitting three separate and independent comments.

(1) These comments address only reduction and prevention of oral health problems claim in OTC oral antiplaque drug products. (2) Separate comments address the structure/function claim in

OTC antiplaque products. (3) Separate comments also address the cosmetic claims that are applicable to oral antiplaque products.

WhiteHill agrees with the Division of Dermatologic and Dental Products in the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) that claims for the prevention or treatment of gingivitis are properly classified and evaluated as drug claims. Because of its focus on gingivitis, however, the FDA failed to consider the evidence presented to the Subcommittee with regard to the reduction and prevention of other oral health problem claims justified by reduction of plaque alone, without consideration of any effect on gingivitis, that are also properly classified and evaluated as drug claims. These WhiteHill comments therefore focus solely on the general reduction and prevention of oral health problems benefits of a significant reduction in dental plaque in the absence of a gingivitis endpoint.

Considering the draft Guidance for Industry defines the term, gingivitis, as “plaque-induced gingival disease” that “responds well to oral hygiene and antimicrobial products,” it is disappointing and disconcerting to this member of the oral hygiene industry that the draft Guidance does not expand on the role biofilms play in dental plaque; nor, except for a general reference to “oral hygiene,” does the draft Guidance address the critical role *physical removal of biofilms* plays in maintaining oral health. Accordingly, both of these are covered at length by WhiteHill in the three separate and independent comments included herewith.

WhiteHill manufactures a melt-emulsion of polydimethylsiloxane (silicone) in the food-grade surfactant poloxamer. As demonstrated in scientific studies submitted by WhiteHill to the Subcommittee and in these comments responding to the proposed draft Guidance for Industry with respect to structure/function and oral disease reduction and prevention claims, the combination of polydimethylsiloxane and poloxamer is effective in achieving a significant

reduction in dental plaque. This combination was determined by the Subcommittee to be Category I for safety (pages 32274-32275). Because this combination is not intended for use to prevent gingivitis, it was placed in Category III for this use.

I. The Requested FDA Action

The proposed draft Guidance for Industry properly recognizes the effectiveness of antimicrobial active ingredients in combination with “oral hygiene” in achieving a significant reduction of the gum disease, gingivitis. It fails, however, to provide similar recognition of the effectiveness of active ingredients to achieve a significant reduction of dental plaque, resulting in a reduction and prevention of oral health problems with no claim to a gingivitis endpoint. For the reasons set forth below in these comments, WhiteHill requests that FDA recognize, in the draft Guidance for Industry and in the monograph, the important effectiveness of drug products that achieve a significant reduction in dental plaque with no gingivitis endpoint resulting in the reduction and prevention of oral health problems. Specifically, WhiteHill requests that FDA amend 21 C.F.R. Part 356 in the following four ways.

A. Section 356.3: Definitions

FDA should add a new Section 356.3(q) to define the term “antiplaque drug” as “a drug applied to the oral cavity to help reduce and prevent oral health problems.”

B. New Section 356.17: Antiplaque Active Ingredients

FDA should add a new Section 356.17 in order to list safe and effective antiplaque ingredients. This section should list, as one of these active ingredients, the combination of polydimethylsiloxane and poloxamer, in a ratio ranging from 1:1 to 1:100, used at a concentration ranging from .01 to 4 percent for liquid and gel emulsions, and other oral care

products, and an amount ranging from .01 to 0.2 grams per use for chewing gum, mints, breath strips, and chewable candies<sup>1</sup> provided that the final product must meet the performance test established in new Section 356.94.

C. New Section 356.67: Labeling of Antiplaque Drug Products

The statement of identity should be established as "antiplaque." The indication should be "helps reduce and prevent oral health problems."

D. New Section 356.94: Testing of Antiplaque Drug Products

FDA should specify the following performance test for every product in order to qualify as an effective antiplaque product: A twenty percent reduction in plaque using one of the following protocols.

**1. Protocol for Evaluating Effectiveness of Antiplaque Products to Help Reduce and Prevent Oral Health Problems**

A double-blind crossover design is utilized to minimize variances due to subjects' normal plaque growth rates. An effective group size of 20 to 25 is used, with subjects individually screened for a minimal baseline Plaque Index (PI) of 1.8 (Turesky Modified Quigley-Hein, or similar). Subjects report for baseline examination after having refrained from brushing for 12 hours. After baseline scoring and rubber cup prophylaxis to reduce the PI to zero, subjects are instructed to refrain from brushing or flossing for 48 hours, during which they use the specified test product or placebo at the specified times throughout the day (typically three to six times, depending on the product type). Final PI is scored at 48 hours and the difference is recorded as "reduction in plaque accumulation between brushings" for that test period. Allow at least one week "washout" after the first test period, before the crossover period begins. A

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<sup>1</sup> The limitation recommended by the Subcommittee that antimicrobial antigingivitis should be expectorated and not ingested (transcript for May 29, 1998, page 110) does not apply to these combination ingredients, which the Subcommittee noted are used in food and ingested OTC drug products (pages 32274-32275).

statistically significant, average PI reduction of at least 20 percent over the placebo is required to satisfy the criterion of helping reduce and prevent oral health problems.

**2. Protocol for Evaluating Effectiveness of Antiplaque Products to Help Reduce and Prevent Oral Health Problems**

A double-blind crossover design is used to minimize variances due to subjects' normal plaque growth rates. An effective group size of 20 to 25 is used, with subjects individually screened for a minimal baseline PI of 1.8 (Turesky Modified Quigley-Hein, or similar). Subjects report for baseline examination after having refrained from brushing for 12 hours. After baseline scoring and rubber cup prophylaxis to reduce the PI to zero, subjects are instructed to continue their normal brushing habits, but not use any mouth rinses, mints, or gums during the test period. Test periods should be not less than 14 days, preferably 30 days. During the test the subjects use the specified product or placebo at the specified times throughout the day (typically three to six times, depending on the product type). Final PI is scored and the difference is recorded as "reduction in plaque accumulation over normal oral hygiene". Allow at least two weeks "washout" after the first test period, before the crossover period begins. A statistically significant, average PI reduction of at least 20 percent over the placebo is required to satisfy the criterion of helping reduce and prevent oral health problems.

**II. The Role of Dental Plaque in Helping to Reduce and Prevent Oral Health Problems**

**A. The Determinations of the Subcommittee**

In its report of May 29, 2003 to FDA, the Subcommittee has made a number of extremely important determinations relating to plaque (pages 32236-32239) that directly support the crucial importance of plaque in the role of oral health problems.

The Subcommittee begins by pointing out that “Plaque has a critical etiological role in the development of dental caries, gingivitis, and periodontal disease.” These are, of course, the three primary oral health problems that are endemic throughout the United States. Unfortunately, the Subcommittee failed to pursue this scientific determination to the logical conclusion that reduction of dental plaque will help reduce and prevent these serious oral health problems. The FDA, in their draft Guidance for Industry, is hereby requested to pursue this scientific determination to the logical conclusion that reduction of dental plaque will help reduce and prevent these serious oral health problems.

As the Subcommittee recognized, there is wide variation in the composition of dental plaque among individuals. Plaque differs both qualitatively and quantitatively in its bacterial content. The Subcommittee stated that:

“This difference in bacterial composition has a major effect on its pathogenic potential both for periodontal diseases and caries. Some dental plaques are not pathogenic or associated with disease, whereas others are etiologic factors for caries and periodontal diseases. However, the two types of plaque cannot be distinguished visually.”

Accordingly, the Subcommittee determined that “It may be prudent to treat all plaques as having pathogenic potential.”

WhiteHill agrees completely. All dental plaque is a risk factor for oral health problems. Reduction of dental plaque is therefore of vital importance in helping to reduce and prevent oral health problems. The FDA is hereby requested, in their draft Guidance for Industry, to treat all plaque as having pathogenic potential.

The Subcommittee went on to state that nonspecific plaque control is essential to the prevention and reduction of oral health problems:

“‘Nonspecific’ plaque control involves decreasing the entire microbial mass in a nonspecific manner, *i.e.*, without any attempt at differentially removing or suppressing any particular bacterial species, although shifts in bacterial composition may occur.”

The Subcommittee specifically noted that nonspecific control of dental plaque “needs to be thorough in order to achieve clinically significant therapeutic benefits” and observed that the degree of plaque reduction must be both clinically significant and statistically significant for it to be determined to be effective.

Once again, WhiteHill agrees. In order to be regarded as effective in reducing and preventing oral health problems, an antiplaque product must meet a pre-established degree of reduction in dental plaque determined to be clinically significant as determined using a standardized validated clinical protocol. Contrary to the position of the FDA, WhiteHill maintains such reductions in dental plaque can be affected without the use of antimicrobials.

The action requested by WhiteHill in Part I of these comments meets these criteria.

**B. Other Dental Authorities Agree with the Subcommittee and WhiteHill that All Dental Plaque Must Be Considered as Having Pathogenic Potential**

The published dental literature is filled with articles and books that document the pathogenic potential of dental plaque. The following quotations are merely representative of this huge body of professional opinion.

“The accumulation of bacterial biofilms on tooth surfaces results in two of the most prevalent infectious diseases of man - caries and periodontal diseases.”<sup>2</sup>

“The importance of daily plaque removal is underscored by the fact that in the absence of plaque, no caries, gingivitis or periodontal disease can occur.”<sup>3</sup>

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<sup>2</sup> M. Wilson & J. Pratten, Laboratory Assessment of Antimicrobials for Plaque-related Diseases, *in* (H.N. Newman & M. Wilson, eds.) Dental Plaque Revisited 503 (1999).

<sup>3</sup> D.E. Willmann & E.S. Chaves, The role of dental plaque in the etiology and progress of inflammatory periodontal disease, Primary Preventative Dentistry Publ., 1999, at 72.

A bibliography of additional scientific literature that supports these types of statements is included in Appendix A to these comments. A number of these articles and book chapters were authored by the members of the Subcommittee.

C. Reduction of Plaque in the Absence of a Gingivitis Endpoint is a Therapeutic Objective in Order to Reduce and Prevent Oral Health Problems

As the Subcommittee and the published literature recognize, all dental plaque must be regarded as having pathogenic potential. Likewise, the FDA is expected to recognize the pathogenic potential of all dental plaque in its draft Guidance for Industry. Drug products that achieve a statistically significant and clinically significant reduction in dental plaque are therefore appropriately to be recognized by the FDA as effective in helping to reduce and prevent oral health problems. Thus, the remaining question is what type of performance testing should be required in order to assure the FDA that an antiplaque drug product reduces dental plaque by an amount that is both statistically and clinically significant. WhiteHill recommends that the performance tests described above in Part I(D) be adopted.

III. The Combination of Polydimethylsiloxane and Poloxamer is Safe and Effective in the Reduction of Dental Plaque

As the Subcommittee recognized in its report (page 32274), the combination of polydimethylsiloxane and poloxamer has been used in a number of different formulations, including sprays, mouthwashes, dentifrices, and chewing gum. The Subcommittee accepted this combination as Category I for safety, *i.e.*, generally as recognized as safe. The Subcommittee did not review this combination (or any other ingredients) for antiplaque effectiveness alone, because of its position that only ingredients that are proved effective against gingivitis should be included in the monograph. As noted in Part I(B) of these comments, the ratio of the polydimethylsiloxane to the poloxamer varies from 1:100 in mouthwashes to 1:1 in chewing

gum. The concentration of the combination ranges from 0.4 percent to 4 percent for liquid and gel emulsions, including toothpaste and other oral health products, and the amount used in products like chewing gum, mints, breath strips, and chewable candies ranges from .01 grams to 0.2 grams per use. Each formulation will vary depending upon the precise characteristics of the product involved. Accordingly, it is essential that the FDA draft Guidance for Industry and the monograph establish a performance test, of the type described above in Part I(D) of these comments, in order to assure consistent effectiveness in the reduction of plaque in the absence of a gingivitis endpoint.

WhiteHill has conducted several clinical studies, using a variety of dosage forms and product formulations, that demonstrate that this combination of ingredients can be formulated in a way that achieves the standard of clinical effectiveness by a twenty percent reduction in dental plaque, using the type of protocol set forth above in Part I(D) of these comments. In the following paragraphs, we briefly summarize the protocols and results of this testing. The clinical study reports were included as Appendix B to WhiteHill's November 24, 2003 response to the Subcommittee findings.

A. Clinical Research Protocol WHLS - 005

This clinical study examined the effect of frequent daily use of polydimethyl siloxane and poloxamer, in sorbitol-based sugar-free mints, in reducing dental plaque between brushings. The study employed a double-blind crossover design with several different formulations of the test product, and a placebo. It followed the protocol described in Section I(D)(1) of these comments, except for a lower number of subjects (n=10).

The subjects were instructed to dissolve one mint at each of six prescribed times (after each meal, between meals, and at bedtime). The results for the three most effective mint

formulations, incorporated at 1.5 percent in the mints with polydimethylsiloxane having  $0.6 \times 10^6$  cs and  $2.5 \times 10^6$  cs viscosity respectively, were:

Product	PI at Baseline*	PI 48 Hour	< PI Vs. 48 hr Placebo	% Change Vs. 48 hr Placebo	Statistical Significance versus Placebo
<b>Placebo Mint</b>	2.12	2.30	---	---	---
<b>Test Mint A</b> 0.6 X 10 <sup>6</sup> cs 1.4 mg PDMS	2.01	1.61	-0.69	-30.0	p < 0.0001
<b>Test Mint B</b> 2.5 X 10 <sup>6</sup> cs 1.4 mg PDMS	2.08	1.57	-0.73	-31.7	p < 0.0001
<b>Test Mint C</b> 2.5 X 10 <sup>6</sup> cs 0.7 mg PDMS	2.14	1.49	-0.81	-35.2	p < 0.0001

\* No statistical difference between baseline readings.

These results clearly demonstrate a statistically and clinically significant difference in the reduction of the accumulation of dental plaque between the placebo mint and the three most effective formulations of test mints. This reduction in dental plaque is sufficient to help reduce and prevent oral health problems.

**B. Clinical Research Protocol WHOTI G-040**

This clinical study examined the effect of frequent daily use for four weeks of polydimethylsiloxane and poloxamer in a chewing gum in reducing dental plaque accumulation while maintaining normal brushing habits. The study employed a three group double-blind crossover design with a test product, a chewing gum placebo, and a mint placebo. It followed the protocol described in Section I(D)(2) of these comments, using 21 subjects.

The subjects were instructed to chew one piece of gum after each meal (three per day). The tested gum formulation contained 1.5 percent of the drug with polydimethylsiloxane having  $2.5 \times 10^6$  cs viscosity equivalent to 1.4 mg per piece. In addition to a chewing gum

placebo group, a mint control group was also included in this study as a second placebo to assure that chewing action was not a significant factor. There was no significant difference between the mint control and the placebo gum. There was, however, a significant difference between the mint control and the test gum.

The results, summarized in the table below, clearly demonstrate a statistically and clinically significant difference in the reduction of the accumulation of dental plaque between the placebo gum and the test gum. This reduction in dental plaque is sufficient to help reduce and prevent oral health problems:

Product	Initial PI Baseline	Final PI Day 28	< PI Vs. 28 day Placebo	% Change Vs. 28 day Placebo	Statistical Significance <i>versus</i> Placebo
Placebo Gum	2.18	2.25	---	---	---
Test Gum 1.5% emulsion 1.4 mg PDMS	2.18	1.48	0.77	34.2	p < 0.0001

C. Clinical Research Protocol WHOTI G-041

This clinical study was a repeat of WHOTI G-40, described above, using the same placebo gum and test gum formulations. A mint control was not employed in the G-041 study. The results from this study, summarized in the table below, confirm the findings from the WHOTI G-40 trial of statistical and clinical significance in helping to reduce and prevent oral health problems:

Product	Initial PI Baseline	Final PI Day 28	< PI Vs. 28 day Placebo	% Change Vs. 28 day Placebo	Statistical Significance <i>versus</i> Placebo
Placebo Gum	2.28	2.28	---	---	---
Test Gum 1.5% emulsion 1.4 mg PDMS	2.18	1.40	0.88	38.6	p < 0.0001

D. Rawhide Study in Dogs

A rawhide chew-treat study examining the effect of polydimethylsiloxane and poloxamer in reducing dental plaque in dogs was published in the Proceeding of the 1994 World Veterinary Dental Congress.<sup>4</sup> Rawhide is the nearest animal equivalent to human chewing gum. The published article does not chemically identify WhiteHill's mixture because of sponsor trade secret concerns that existed in 1994. Instead, the study sponsor accurately described the drug by function as one which:

"interrupts the formation of plaque by coating the teeth with a smooth thin film that prevents materials from adhering to tooth surfaces."

The rawhide chew treat study used a protocol similar to the human chewing gum studies described in Section I(D)(2) of these comments, using 18 dogs. The dogs were divided randomly into three groups of six dogs each. The first group received no treatment, the second group received untreated rawhide (placebo), and the third group received treated rawhide. The coated treats contained approximately 200 mg of the mixture per chip.

The dogs were scored for plaque using an animal-suitable modification which combined the Silness-Loe Plaque Index (1964) for the low scores of 0-3 and the Turesky Modified Quigley-Hein Plaque Index for scores of 4-5. After an initial prophylaxis to reduce plaque to zero, dogs in groups two and three were given three of the assigned treats per day and plaque scores were evaluated bi-weekly for 24 weeks. The authors summarized the results of the study:

"plaque and tartar build-up on cleaned teeth was significantly less for dogs chewing coated treats than for dogs offered placebo treats, the reduction ranging from 24-32% for plaque . . . ."

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<sup>4</sup> M.L. Sharp, et. al., A test method to evaluate the efficacy of a formulation on plaque, tartar and mouth odor in dogs, Proc. World Vet. Dent. Congress 82-84 (1994).

These results clearly demonstrate a statistically and clinically significant difference in the reduction of the accumulation of dental plaque between the placebo treat and the coated treat. This reduction in dental plaque is sufficient to help reduce and prevent oral health problems.

In light of the results of these human and animal studies, FDA should accept the combination of polydimethylsiloxane and poloxamer as one of the safe and effective antiplaque ingredients that will be listed under the new section of the monograph requested in Part I(B) of these comments and in an expanded version of the FDA's draft Guidance for Industry.

IV. Conclusion

For the reasons set forth above, WhiteHill requests that FDA recognize that the combination of polydimethylsiloxane and poloxamer is Category I to help reduce and prevent oral health problems, in accordance with the conditions established in Part I of these comments.

  
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Robert D. White