

WhiteHill Oral Technologies, Inc.

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
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Draft Guidance for Industry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)
General Comments

Set out below are General Comments from WhiteHill Oral Technologies, Inc.

(WhiteHill), Stafford, Texas, the developer and manufacturer of OTC oral care ingredients for controlling plaque (biofilms) and OTC and Rx interproximal devices, which help control: plaque, gingivitis, periodontitis and periostasis.

Background:

WhiteHill is the developer and manufacturer of the proprietary OTC antiplaque ingredient, MICRODENT®. MICRODENT® reduces plaque buildup, *not by antimicrobial action*, but rather *by physical chemistry means*, where an ablative, physical coating is formed on tooth surfaces that reduces the surface-free energy of tooth surfaces, thereby disrupting plaque adhesion. MICRODENT® was not intended to claim a gingivitis endpoint attributed to antimicrobial action.

WhiteHill filed a response on June 17, 1991, to the FDA original call-for-data of September 19, 1990, for *plaque* and gingivitis ingredients (as reported in the Federal Register 55, No. 182 FR 38561, Proposed Rules). WhiteHill qualified MICRODENT® for review by the Subcommittee. Clinical data reporting up to 35% *plaque reduction* for the antiplaque ingredient, MICRODENT®, in various carriers ranging from breath sprays and gels, to breath mints and chewing gum, was reviewed by the Subcommittee. Absent clinical data on gingivitis endpoints, the Subcommittee classified MICRODENT® as needing further information to make a decision.

On November 24, 2003, WhiteHill filed several responses to the Subcommittee's tentative final report published May 29, 2003 (Federal Register 68 FR 32232). These responses were entitled:

- “Comment: Cosmetic Claims for Oral Antiplaque Products”
- “Comment: Reduction and Prevention of Oral Health Problems Claim in OTC Oral Antiplaque Drug Products”
- “Comment: Structure/Function Claim for OTC Oral Antiplaque Products”

Clarification Called For:

The following is cited at Section II.B. “Antigingivitis Rulemaking” of the June 28, 2005 Draft Guidance published by the FDA to aid drug sponsors:

During the past several decades, many products have entered the marketplace as OTC products that purport to treat or prevent gingivitis. As a result of the proliferation and promotion of those products, FDA convened a subcommittee of the Dental Products Panel (Subcommittee) in 1993 to evaluate OTC products that make *gingivitis claims* and that were in the marketplace without an NDA. The panel reviewed the data submitted for the antigingivitis products and reported its findings on the safety and effectiveness of OTC ingredients for the reduction or prevention of gingivitis. (emphasis added)

The reference to gingivitis claims by the FDA is not accurate.

The original call-for-data was made for OTC products that made *plaque* and gingivitis claims. See copy of September 19, 1990 FDA call-for-data (enclosed). WhiteHill made “plaque-only” claims and, as such, qualified for Subcommittee review in 1993. The WhiteHill “plaque-only” claims did not fit the Subcommittee’s agenda of requiring a gingivitis endpoint for controlling plaque buildup.

The Subcommittee’s final report on May 29, 2003, chose not to recognize the evolution of plaque to a biofilm nor the validity of “plaque-only” claims. WhiteHill challenged the Subcommittee findings in the three responsive filings of November 24, 2003, referenced above.

Plaque-Induced Gingivitis:

The Draft Guidance “Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention” published June 28, 2005, addresses plaque-induced gingivitis.

Query: Where does that leave plaque buildup that does not have a gingivitis endpoint?

Specifically, how does the FDA propose to handle “*plaque-only*” claiming ingredients such as described in the referenced November 24, 2003 WhiteHill submissions?.

Since MICRODENT® was first presented to the Subcommittee in 1991 as a “plaque-only” ingredient, the role of plaque as a biofilm that hosts pathogens which cause gingivitis and gum disease has been expanded by oral care researchers to include hosting pathogens that exacerbate chronic diseases, such as Type II diabetes, heart disease, osteoporosis, etc. Oral hygiene researchers report that controlling plaque buildup (biofilm) and its associated pathogens, per sé, could have distinctive “endpoints” beyond gingivitis, i.e. controlling glycosylated hemoglobin levels, controlling carotid artery thickness, etc. (see the publications of Genco, Desvarieux, etc.). Moreover, biofilm in whatever form it takes, is present, i.e. fresh plaque, mature plaque, calcified plaque (i.e. tartar), etc., without a gingivitis endpoint continuum to pose a potential threat to oral

health due to the pathogens hosted therein. To single out only those biofilms with a gingivitis endpoint, and to ignore biofilms without gingivitis endpoints or with endpoints other than gingivitis, is clearly not in the public's best health interests.

It is well established that plaque (biofilm) hosts pathogens throughout all levels of accumulation (biofilm buildup), and as such, starting with its initial formation, biofilm poses an ongoing threat to oral health. Accordingly, non-antimicrobial ingredients that help control biofilm buildup without a specific disease endpoint can contribute to oral health. Several levels of biofilm buildup that do not have a gingivitis endpoint and therefore fall outside the Guidance, include:

- (1) Biofilm accumulation hosting pathogens but levels *less than that* required to effect gingivitis,
- (2) Biofilm accumulations sufficient to support gingival detachment less than 5mm without bleeding sites,
- (3) Biofilm accumulations that influence periostasis, and
- (4) Biofilm accumulations sufficient to exacerbate indications of various chronic diseases such as Type II diabetes, heart disease, osteoporosis, as well as low-birth-weight babies of expectant mothers.

“Oral Hygiene” Falls Short of *Physical Removal of Biofilms*:

The accepted means for effectively controlling biofilms is to frequently *physically* remove and/or *physically* disrupt them. This *physical removal/disruption* is much more specific and demanding than the term “oral hygiene” presently relied on by the FDA in the draft Guidance for Industry, i.e. “plaque induced gingivitis responds well to oral hygiene and antimicrobial products.” Topical chemotherapeutic treatment of biofilms without specific

accompanying *physical removal/disruption* is simply not effective. Thus, topical application of “antigingivitis chemotherapeutic ingredients” must be accompanied by *physical removal/disruption* of biofilms. Citing “oral hygiene” as the means for such physical removal is not only vague; it lacks the specificity required to handle biofilm. See the work of Socransky and others in enclosed Comment: Structure/Function Claim for OTC Oral Antiplaque Products.

“Oral hygiene” generally defines “cleaning” of tooth surfaces, which does not necessarily include physical abrasion and removal of biofilms. *Cleaning* is clearly a cosmetic term and, by statute, is not regulated by the FDA under OTC drug provisions.... yet oral hygiene is a key element in the draft Guidance for drug treatment of gingivitis.

Conclusion:

Clarification of the foregoing is in order.



Robert D. White

Encl: Federal Register 55, No. 182 FR 38561, Sept. 19, 1990