

Plaque Labeling

2.A. *Should an antigingivitis active ingredient that has not demonstrated effectiveness in reducing plaque be allowed to bear labeling statements relating to plaque reduction?*

Procter & Gamble believes strongly that an agent that provides a clinically significant gingivitis benefit by reducing plaque pathogenicity irrespective of its effect on plaque mass is clearly achieving its therapeutic effect through an antiplaque mechanism. Therefore, a statistically significant reduction in plaque mass, plaque virulence or plaque bacterial composition, by an agent that provides a clinically significant reduction in gingivitis, should all be considered as viable support for an antiplaque therapeutic claim relating to “plaque control”. As such, these products should be allowed to bear labeling statements relating to plaque reduction and/or plaque control.

Data presented to the Subcommittee included antigingivitis ingredients with apparent variations in their mechanism of actions – specifically their effects on the growth and/or metabolic activity of plaque. One question from the Agency is whether active ingredients should be differentiated on the basis of the known mechanism of their antiplaque actions, that is, should ingredients which demonstrate gingivitis control through variable effects on dental plaque quantity, metabolism or microbial composition carry similar labeling describing ‘plaque reduction’ as a clinical effect? We believe that the data support labeling the indication of ‘plaque reduction’ as a mechanism for action for all recommended Category I recommended agents of this rulemaking.

The first point in support of this position is that all of the Category I ingredients under consideration (cetylpyridinium chloride, stannous fluoride and essential oils)

provide antigingivitis effects through their direct actions in controlling or modulating dental plaque. However, these ingredients clearly differ in their specific actions on plaque. For example, the data supporting essential oils showed modest general reductions in the levels of plaque in large-scale clinical studies but little data in the way of effects on plaque metabolic activity. The data supporting stannous fluoride revealed low apparent effects on plaque accumulation in the large-scale clinical setting but quite substantial effects on various plaque metabolic processes. The data supporting CPC showed strong effects on both plaque accumulation in a large-scale clinical setting and plaque metabolic activity. All ingredients therefore demonstrated antiplaque effects; they simply differed in the effects observed in different clinical settings and assayed parameters. The rationale for this variation may be related to specific mechanism of actions or possibly potential artifacts in clinical designs, but the important point is that all ingredients provide efficacy through a route of plaque control.

A second point in supporting an 'inclusive' plaque control labeling for all Category I ingredients in this rulemaking is that neither professional or research experts can define the specific antiplaque actions of most importance to the prevention or treatment of gingivitis. In the ANPR preamble the Subcommittee stated:

.....“gingivitis is associated with an accumulation of plaque along the gingival margin but [the Subcommittee] is unaware of any evidence that shows that there is a close correlation between the amount of plaque and the induction of gingivitis, as can be assessed using present day methods. It should be noted that the relationship between the quantity of plaque present and the degree of gingivitis is sufficiently complex such that reductions in plaque mass alone are

*inadequate to conclude that a therapeutic effect on gingivitis could be expected*¹ (emphasis added).....

Furthermore the Subcommittee acknowledged:

... “[we are] unaware of any studies where the volume, mass or amount of plaque can be closely equated with the extent of gingival inflammation.”².....

From the foregoing, it is clear that the Subcommittee agreed that while there is an unambiguous association between plaque formation and gingivitis, there is a much more tenuous correlation between plaque amount, metabolic activity or empirically derived virulence factors with the disease itself.

Procter & Gamble agrees that chronic gingivitis is a disease caused by the effects of dental plaque. The localized actions of dental plaque promote chronic and acute host responses resulting in the cascade of sequelae associated with gingivitis: redness and gingival bleeding. Although the development (prevalence) of gingivitis is clearly dependent upon the formation, development and maturation of dental plaque, the severity of gingivitis cannot be easily and generically predicted by plaque quantity or even plaque quality. That is, in some patients relatively small quantities of plaque promote significant levels of gingivitis. In other patients, fairly high levels of plaque may be associated with only minor development of gingivitis. Examples include higher gingivitis response to plaque in juvenile periodontitis patients and the lower gingivitis response to plaque in smokers. The reason for the variable response of patients to plaque levels is likely related to both host immunological factors and to variable pathogenicities of developed plaques.

¹ Federal Register. 68(32237), May 29, 2003.

² Ibid.

Support for the variable pathogenicity of developed plaques is widespread. A large body of microbiological research has in fact concentrated on the elucidation of more specific aspects of plaque microbiology which may contribute to pathogenicity and may promote strategies toward the chemotherapeutic control of gingivitis. Virulence factors which may be associated with plaque pathogenicity include types of microbial species in plaque³ and variable metabolic products of plaque including ammonia⁴, lipopolysaccharides^{5,6,7}, short chain fatty acids^{8,9,10} and a variety of lytic enzymes^{11,12,13}.

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- ³ Marsh & Martin, Oral Microbiology, 3rd Ed., Chapter 7, pp. 167-197, 1992.
- ⁴ Rizzo, A.A.: Rabbit Corneal Irrigation as a Model System for Studies on the Relative Toxicity of Bacterial Products Implicated in Periodontal Disease. The Toxicity of Neutralized Ammonia Solutions. *J. Periodont.*, 38: 491-499, 1967.
- ⁵ Mergenhagen, S.E.: Endotoxic Properties of Oral Bacteria as Revealed by the Local Shwartzman Reaction. *J. Dent. Res.* 32: 267-272, (1960).
- ⁶ Hofstad, T.: Antibodies Reacting with Lipopolysaccharides from *Bacteriodes melaninogenicus*, *Bacteriodes fragilis*, and *Fusobacterium nucleatum* in Serum from Normal Human Subjects. *J. Infectious Diseases.* 129: 349-352, 1974.
- ⁷ VanDyke, T.E. and W.B. Zinney: Biochemical Basis for Control of Plaque-Related Oral Diseases in the Normal and Compromised Host: Periodontal Diseases. *J. Dent. Res.*, 68: 1588-1596, 1989.
- ⁸ Socransky, S.S. et al.: Morphological and Biochemical Differentiation of Three Types of Small Oral *Spirochetes*. *J. Bacteriology*, 98: 878-882, 1969.
- ⁹ Loesche, W.J. and S.S. Socransky: *Bacteriodes Oralis*, Proposed New Species Isolated from the Oral Cavity of Man. *J. Bacteriology*, 88: 1329-1337, 1964.
- ¹⁰ Montgomery, R.E. et al.: Relation Between Plaque Butyrate Product and Reversal of Gingivitis. *J. Dent. Res.*, 61: 260, 1982.
- ¹¹ Schultz-Hautd, S.S. et al.: Bacterial Factors in Nonspecific Gingivitis. *J. Dent. Res.*, 33: 454-458, 1954.
- ¹² Soder, P. and G. Frostell: Proteolytic Activity of Dental Plaque Material. I. Action of Dental Plaque Material on Azocoll, Casein and Gelatin. *Acta Odont Scand.*, 24: 501-515, 1954.

To be clear, the debate of researchers over specific or non-specific plaque etiologic contributions to gingivitis suggests that the effects of many of the factors cited above (and presumably many others that have not yet been identified) contribute to the pathogenicity of dental plaque in inducing gingivitis. Further, in the absence of specific etiological significance to plaque effects, the development of distinct labeling is not helpful to either patients or professionals. In fact, if distinct labeling is developed excluding stannous fluoride from making 'prevent plaque' claims, then one might argue that the recommended antiplaque labeling should be modified for the other Category I ingredients to describe their explicit effect on plaque given they lack similar efficacy for specific microbiologic or metabolic effects.

The last supporting argument for the adoption of single encompassing labeling to stannous fluoride are the results of recent clinical studies using state of the art methods for the quantitative evaluation of plaque inhibitory effects. The labeling indication for stannous fluoride recommended by the Subcommittee was based primarily on observed efficacy in long-term clinical trials of stannous fluoride dentifrices which showed clear antigingivitis efficacy. In these studies, plaque effects for stannous fluoride averaged less than 10%. Data from various *ex vivo* plaque assays, in particular PGRM, revealed that stannous fluoride had substantial effects on plaque microflora, plaque metabolism and on inhibiting the growth of plaque bacteria. On this basis, the Subcommittee argued for a specific explanatory addition to the stannous fluoride indication related to metabolic effects. Most recently, the application of improved clinical test methods has clearly revealed significant efficacy for stannous fluoride in reducing plaque accumulation in the clinical setting – to complement actions in reducing plaque metabolic activity. In these studies, careful assessments of plaque development in populations controlled

¹³ Thonard, J.C. et al.: Neuraminidase Activity in Mixed Culture Supernatant Fluids of Human Oral Bacteria. *J. Bacteriology*, 89: 924-925, 1965.

for hygiene and diurnal growth effects have revealed substantial efficacy for stannous fluoride in the prevention of plaque mass accumulation *in vivo*. [The model used in these determinations – the Digital Plaque Image Analysis Repeat Measures (DPIARM)– and data supporting the effects of stannous fluoride are described in Section 3.A. herein]. It is noteworthy that the DPIARM shows efficacy for all of the approved Category I ingredients and also for triclosan dentifrices and chlorhexidine mouthrinses. These new results cumulatively support an antiplaque action for stannous fluoride which is not just restricted to metabolism or specific microbiological effects, but includes plaque mass reductions in a more traditional context. While the rationale for the unusually low effects of stannous fluoride on plaque removal in longer-term clinical studies is not clear, it is possible that this is related to potential artifacts in evaluating plaque in large-scale populations. Most importantly, these results demonstrate that stannous fluoride cumulative actions on plaque are not substantively dissimilar from other Category I recommended ingredients, CPC and essential oils.

Furthermore, effective antimicrobials clearly achieve therapeutic effects through an antiplaque mechanism – the only question is whether the antimicrobial effects are manifested as gross differences in plaque growth potential or more subtle (and less visible) effects on plaque pathogenicity. Importantly, it is expected that the oral pharmacology of antimicrobial antigingivitis agents can be adequately measured whether the primary mechanism or known impact of ingredients on the plaque is metabolic, microbiological or on plaque mass development respectively.

To summarize, although it is widely accepted that supragingival plaque is associated with gingivitis, the precise etiology of the disease is not completely understood. Certainly, the causal effects of plaque on gingivitis are multifactorial. Non-chemotherapeutic approaches to treating the disease include hygiene or professional plaque removal procedures. In these instances it is assumed that all plaque is ‘bad’ and that the nonspecific removal or reduction in the biofilm results in the elimination

of not only the plaque, but also any other specific microbiological or metabolically derived causative agents. An alternative hypothesis exists within the literature that suggests that gingivitis may be a result of specific bacteria that reside within the supragingival biofilm and it is the abundance of these specific organisms and their proximity to the gingiva that is responsible for the disease.¹⁴ The selective elimination of these organisms or their virulence factors, which likely constitute a smaller fraction of the whole biofilm, would clearly influence the disease, yet may not be measurable as an equivalent reduction in plaque mass, due to the low sensitivity of current visual and tactile clinical measures. Chemotherapeutic measures may be expected to produce alternative effects such as the specific inhibition or elimination of the causative agent and these may account for an improvement in the disease state with quite variable proportional reductions in plaque mass. We submit that different approved active ingredients that provide a significant and clinically meaningful reduction in gingivitis, albeit with differential efficacy on plaque composition or virulence should be allowed to similarly label for an unqualified 'antiplaque' effect in both the statement of identity, as well as the indication ("uses") section of the labeling.

¹⁴ Loesche, W.J.: Chemotherapy of Dental Plaque Infections. *Oral Science Review*, 9: 65-107, 1976.