

Procter & Gamble

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

Re:Docket No. 2005D-0240, Draft Guidance
to Industry, "Gingivitis: Development and
Evaluation of Drugs for Treatment or
Prevention"

Dear Sir or Madam:

The Procter & Gamble Company, a leader in dental and oral care products, respectfully submits these comments in response to the Draft Guidance for Industry entitled "Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention" published June 28, 2005, in the *Federal Register* (FR Doc 05-12764). As the manufacturer of the Crest[®], Scope[®], Oral-B[®], and Glide[®] family of oral care products, Procter & Gamble has a significant interest in the development of this guidance.

Procter & Gamble's long history in the research, development and marketing of antigingivitis/antiplaque products has led to many technological advances in the dental area, including: 1) development of Peridex[®] Oral Rinse, the first prescription product approved via an NDA for treatment of gingivitis in 1986; 2) the development and marketing of Crest[®] Gum Care, a stannous fluoride product for mitigation of plaque and gingivitis, and; 3) the development of Crest[®] Pro-Health Rinse containing cetylpyridinium chloride (CPC) which is specially formulated for the treatment and prevention of plaque and gingivitis. Additionally, Procter and Gamble provided extensive data to the Plaque and Gingivitis Subcommittee on stannous fluoride and CPC which resulted in these two active ingredients being recommended for Category I status in the Antigingivitis/Antiplaque Advanced Notice of Proposed Rulemaking.

In our comments Procter & Gamble will address several aspects of the proposed draft guidance, including proposed primary and secondary clinical endpoints, in particular the relegation of bleeding to a secondary endpoint, the proposed standard of care, the prescribed subject population and the absence of consideration that a reduction in plaque can be represented as something more than a decrease in plaque mass, area or volume.

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Our comments are organized into five sections within this document:

1. Bleeding is an appropriate stand-alone primary endpoint in gingivitis trials.
2. Standard of care should not confound the results of a clinical trial.
3. Proof of effectiveness should be assessed in a population with a narrow level of disease that can be extrapolated to the general OTC population.
4. Plaque index represents not only a reduction in plaque mass, area, and volume but other assessments of plaque control as well.
5. General Comments and Considerations

Respectfully submitted on behalf of The Procter & Gamble Company



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Executive Summary of Procter & Gamble's Comments to the Guidance for Industry Related to the Development and Evaluation of Drugs for the Treatment and Prevention of Gingivitis

Bleeding is an appropriate stand-alone primary endpoint in gingivitis trials

The draft guidance, as written, allows for the assessment of gingivitis based on a primary endpoint, gingival index. In addition to visual characteristics (color, tissue form, and texture), gingival bleeding is a widely recognized characteristic of gingivitis. The draft guidance permits the use of indices for the assessment of gingivitis that incorporate visual characteristics with bleeding (Löe and Silness Gingival Index) and visual characteristics alone (Modified Gingival Index). Procter & Gamble respectfully requests that the Agency include gingival bleeding as a stand-alone primary endpoint for the clinical determination of gingivitis and permit indices that measure bleeding alone as acceptable assessments of gingivitis.

Standard of care should not confound the results of a clinical trial

The draft guidance suggests that the standard of care for a clinical trial designed to assess the effectiveness of a drug should include flossing. Although P&G agrees flossing is a recommended standard of care for good oral health, flossing is not a regular practice for a significant proportion of the general population. The introduction of a "flossing routine" to a study population following baseline balance and randomization has the propensity to confound the trial outcome. Furthermore, the inclusion of flossing would make trial design and interpretation extremely difficult, if not impossible, considering the majority if not all historical gingivitis trials have been conducted in the absence of flossing, including those studies upon which the current American Dental Association guidelines and recommendations for clinically-significant outcomes have been based. Procter & Gamble respectfully requests the Agency modify the guidance relative to standard of care (Section V. E.) to read, "regular brushing and continuation of any existing manual oral care habits (e.g. flossing)".

Proof of effectiveness should be assessed in a population with a narrow level of disease that can be extrapolated to the general OTC population

The Agency recommends that "products intended to be marketed OTC be assessed in a population that includes a full range of gingivitis". There is no evidence to suggest that the etiology or mechanism of plaque-induced gingivitis differs with severity of gingivitis; therefore, the effect of a treatment can be generalized. Two of the most important considerations for an OTC study population are 1) that a sufficient amount of disease exists to demonstrate a treatment effect and 2) the results from a study population can be generally applied to the OTC population for which the product under study is intended. Procter & Gamble recommends that a product intended to be marketed OTC be studied in a population which is appropriate for determining anti-gingivitis efficacy and for generalizing the efficacy to the OTC population.

Plaque index represents not only a reduction in plaque mass, area, and volume but other assessments of plaque control as well

Gingivitis is clearly associated with the accumulation of dental plaque along the gingival margin. The specific relationship between plaque and gingivitis is still not known. Although reductions in plaque mass, area, and volume can result in reductions in gingivitis this is not the only mechanism by which plaque can be controlled and result in a gingivitis benefit. Procter & Gamble requests that the guidance be modified to include not only plaque reduction but, in addition, other meaningful measures of plaque control (e.g. a reduction in plaque glycolysis and an inhibition of plaque re-growth, reduction in metabolic factors of specific pathogenic bacteria, a decrease in specific pathogenic bacteria, etc.).

General Comments and Considerations

Although there are a number of indices used for the assessment of gingivitis the ideal index should be simple, sensitive, reliable, objective, and quantitative without being time consuming or cost prohibitive. Procter & Gamble suggests the Agency include a position that promotes the continued development of new measures for the assessment of plaque and gingivitis and provides additional guidance how interested parties can work with the Agency to gain acceptance for these new state of the art methods.

The acceptance of a product, which includes safety, efficacy and esthetics, is certainly an important consideration for the manufacturers of consumer products. The evaluation of all of these parameters in a single trial however increases the risk that the results of the primary therapeutic endpoints will be confounded. In fact inclusion of multiple endpoints can increase study complexity to the point that all endpoints can be confounded. Procter & Gamble suggests the Agency clarify that the evaluation of non-therapeutic endpoints should be considered, however, it is not necessary for this assessment to be done within a pivotal gingivitis trial.

1. Bleeding is an appropriate stand-alone primary endpoint in gingivitis trials

The Draft Guidance specifies primary and secondary endpoints that should be prospectively described in the protocol. The only stand-alone primary endpoint identified, however, is the gingival index (GI), with plaque index (PI) as a potential co-primary endpoint or secondary endpoint. The guidance specifically states that bleeding index is a common secondary outcome variable, and goes on to state that it is not sufficient as a stand-alone primary outcome variable. Procter & Gamble requests that the Agency revise this portion of the guidance to include gingival bleeding as another stand-alone primary endpoint for the clinical assessment of gingivitis.

There are numerous scientific reasons for this request. First, plaque-associated gingivitis is defined as the inflammation of the gingiva. The presence and severity of gingivitis is based on the clinical characteristics of inflammation which include gingival bleeding, redness, edema, loss of tissue form, and gingival tenderness¹. The Agency has acknowledged that there are different ways to assess gingivitis; however, it specifies gingival index as the only single primary clinical endpoint in clinical studies. Although the Löe and Silness Gingival Index (LS GI) is a combination index, measuring both bleeding and the visual signs of inflammation, other gingival indices such as the Modified Gingival Index (MGI) only provide an assessment of appearance changes such as color, texture, and glazing. The draft guidance therefore narrows the determination of gingivitis severity to appearance changes only, and ignores other parameters, such as bleeding, which may be equally or even more indicative of gingival health status. The following comments provide strong evidence that changes in gingival bleeding are as indicative of gingival health as changes in color, texture, and glaze.

¹ H. Löe, and J. Silness (1963) "Periodontal Disease in Pregnancy I. Prevalence and Severity", Acta Odont Scand. 21:533-551.

Bleeding is a reliable, sensitive, and objective measure of gingivitis that can be standardized

Gingivitis is defined in the draft guidance as “an inflammation of the soft tissue of the oral cavity that immediately surrounds each individual tooth.” This includes inflammatory lesions present in the interdental tissue where the visual signs of inflammation could be obscured². The interdental tissue beneath the contact point constitutes a prime site for gingivitis. A gingival bleeding assessment allows for the whole tooth including the tissue hidden from a visual assessment to be scored, thus making bleeding a reliable and complete measure of disease.

It has been reported that both bleeding and redness are early signs of gingivitis^{3,4,5,6}. Muhlemann and Son demonstrated that after 17 days with no oral hygiene, 13 of the subjects exhibited a marked increase in bleeding sites (88 to 470) and a nominal increase in redness (6 to 81). The authors concluded that sulcus bleeding was the first clinical sign of gingivitis occurring as early as day 6⁶. The early detection of bleeding in the absence of color change was confirmed by Hirsch et al., on average at day 6.6⁷. Engelberger et al. demonstrated a positive, statistically significant correlation between both Sulcus Bleeding Index (SBI) and Papilla Bleeding Index (PBI) and the number of

² J. Caton, A. Polson, O. Bouwsma, T. Blieden, B. Frantz, M. Espeland (1988) “Associations Between Bleeding and Visual Signs of Interdental Gingival Inflammation”, *J. Periodontol*, 59:722-727.

³ J. Caton, O. Boouwsma, A. Polson and M. Espeland (1989) “Effects of Personal Oral Hygiene and Subgingival Scaling on Bleeding Interdental Gingiva”, *J. Periodontol*, 60:84-90.

⁴ G. Greenstein, J. Canton, A. M. Polson (1981) “Histologic Characteristics Associated With Bleeding After Probing and Visual Signs of Inflammation”, *J. Periodontol*, 52:420-425.

⁵ H.G. Carter and G.P. Barnes (1974) “The Gingival Bleeding Index”, *J. Periodontol*, 45:801-5.

⁶ H.R. Muhlemann and S. Son, (1971) “Gingival Sulcus Bleeding – A Leading Symptom in Initial Gingivitis”, *Helvetica Odontologica Acta*, 15:105-113.

⁷ R.S. Hirsch, N.G. Clark and G.C. Townsend (1981) “The Effect of Locally Released Oxygen on the Development of Plaque and Gingivitis in Man”, *J. Clin. Periodontol*, 8:21-8.

inflammatory cells in gingival connective tissue upon histomorphometric analysis⁸. An investigation of the histopathology of gingivitis has revealed that changes in the percentage of inflamed connective tissue and vascularity were associated with bleeding indicating an earlier stage of inflammation than color change^{4,9}. Increases in total area, area of inflamed connective tissue and the percentage of inflamed area of the total connective tissue of gingival biopsies have been shown to increase with an increase in LS GI score¹⁰. However, it was observed that there are minimal differences in the area of inflamed tissue between biopsies with an LS GI score of 1 and those with scores of 2¹⁰. Collectively these data support gingival bleeding as an early sign of gingivitis which may in fact occur prior to or concurrent with color change and edema. Conversely, there is little data to support that color change is an earlier event than bleeding or that combined gingival indices such as LS GI more accurately represent the underlying biology than a bleeding index.

The use of bleeding as an indicator of a change in gingival health has the clinical advantage of being a more objective measure than the visual observation of color change or tissue form. Bleeding is either present or absent, while color changes require subjective estimation by the examiner^{11,12}. Gingival bleeding, upon stimulation or

⁸ T. Engelberger, A. Hefti, A. Kallenberger, K.H. Rateitschak (1983) "Correlations Among Papilla Bleeding Index, Other Clinical Indices, and Histologically Determined Inflammation of Gingival Papilla", *J. Clin. Periodontol*, 10:579-589.

⁹ P.G. Cooper, J.G. Caton, A.M. Polson (1983) "Cell Populations Associated with Gingival Bleeding", *J. Periodontol*, 54:497-502.

¹⁰ R.C. Oliver, P. Holm-Pedersen, H Løe (1969) "The Correlation Between Clinical Scoring, Exudate Measurements and Microscopic Evaluation of Inflammation in the Gingiva", *J. Perio Res*, 4:13-21

¹¹ S. W. Meitner, H. A. Zander, H. P. Iker, A. M. Polson (1979) "Identification of Inflamed Gingival Surfaces", *J Clin Periodontol*, 6:93-97.

¹² A. M. Polson and J. M. Goodson (1985) "Periodontal Diagnosis, Current Status and Future Needs", *J. Periodontol*, 56:25-34.

provocation, is widely accepted as a clinical sign of gingivitis^{13,14}. Examination of gingival bleeding points is a routine part of standard oral exams, and dentists commonly ask their patients about bleeding gums as part of their medical/dental history. Importantly, a reduction in gingival bleeding is a more interpretable result, to both the clinician and their patient, than a reduction observed in an index score based on color, thus making it more objective in nature.

With combined indices like LS GI, as many as four distinct examiner styles have been documented, reinforcing the conclusion that combined indices are quite subjective¹⁵. Examiner subjectivity clearly presents significant obstacles in effectively calibrating for multicenter studies. Bleeding indices are generally recognized as being easier to control through the standardization of probing force, angulation and time to bleeding following soft tissue stimulation. Marks et al., using eight examiners, tried to determine the level of standardization and reproducibility for 5 different commonly used clinical indices, (Papilla Bleeding Score (PBS) & LS GI for gingival health and Volpe-Manhold, Lobene, and PI for dental deposits)¹⁶. The results of this research led the authors to conclude that *“for the evaluation of therapeutic effect, PBS is the most sensitive indicator for gingival health, whereas PI is the most sensitive indicator for dental deposits and the combination of these two indices provides a reliable assessment for claiming superiority or equivalence of antiplaque and antigingivitis agents.”*

¹³ G. Greenstein (1984) “The Role of Bleeding upon Probing in the Diagnosis of Periodontal Disease”, J. Periodontol, 55:684-688.

¹⁴ K.S. Kornman (1987) “Nature of Periodontal Diseases: Assessment and Diagnosis”, J. Periodontol, 22:192-204.

¹⁵ S.F. McClanahan, R.D. Bartizek, A.R. Biesbrock (2001) “Identification and Consequences of Distinct Loe-Silness Gingival Index Examiner Styles for the Clinical Assessment of Gingivitis”, J. Periodontol, 72:383-392.

¹⁶ R. G. Marks, I. Magnusson, M. Taylor, B. Clouser, J. Maruniak, W. B. Clark (1993) “Evaluation of Reliability and Reproducibility of Dental Indices”, J. Clin Perio, 20, 54-58.

The Importance of Bleeding in Assessing Gingivitis

As pointed out in the draft guidance, the Agency convened the Dental Plaque Subcommittee (the Subcommittee) in 1991 which was comprised of several oral health care experts. The Subcommittee determined that gingivitis can, in fact, be safely self-treated by the general public provided that the self-treatment does not take the place of professional care. In determining that certain drugs for the treatment and/or prevention of gingivitis could be marketed OTC, the Subcommittee clearly recognized bleeding as a primary sign or symptom of gingivitis that consumers can self-diagnose¹⁷.

“Some signs of gingivitis, such as bleeding, can be identified by lay persons.”

and

“Gingivitis, especially when severe, may be self-diagnosable because people can recognize some of the signs of gingivitis, such as bleeding, gingival discoloration, and swelling...”

Furthermore, the Subcommittee recognized the significance of gingival bleeding to the consumer as they specifically recommended it as an optional stand-alone indication for the labeling of antigingivitis products. The Subcommittee’s recommendation under §356.65 (b) *Indications*, for both (1) and (3)¹⁸,

(1) *“helps ‘control’, ‘reduce’, or ‘prevent’ ‘gingivitis’, ‘gingivitis an early form of gum disease’, or ‘bleeding gums’.”*

or

(3) *“helps ‘control’, ‘reduce’, ‘prevent’, or ‘remove’ plaque that leads to ‘gingivitis’, ‘gingivitis an early form of gum disease’, or ‘bleeding gums’.”*

In section 4.1 of the comments to the Antigingivitis/Antiplaque ANPR submitted by the joint Oral Care Task Group of the Consumer Healthcare Products Association (CHPA) and the Cosmetic, Toiletry, and Fragrance Association (CTFA), the oral healthcare

¹⁷ Federal Register 68(103), May 29, 2003, at page 32237.

¹⁸ Federal Register 68(103), May 29, 2003, at page 32286.

industry as a group recommended that '*bleeding gums*' is an appropriate indication for all proposed Category I antigingivitis and antigingivitis/antiplaque actives¹⁹.

Recently, bleeding was shown by Charles et al.²⁰ to correlate with the index the Agency has used in the draft guidance as the example for gingival indices and recognized as being the most widely used; Löe & Silness Gingival Index. The objective of this study was to evaluate the effectiveness of two oral rinses relative to a placebo control in a 6 month clinical trial. The authors concluded from this study that the two rinses had comparable antiplaque and antigingivitis efficacy. The authors also reported the percentage of bleeding sites per treatment by creating a binary scale for bleeding sites (LS GI score of 2 or 3) and non-bleeding sites (LS GI score of 0 or 1). The authors concluded that the reduction in bleeding sites paralleled the significant reductions in mean LS GI scores achieved in the two treatment groups. Although the authors did not calculate the correlation coefficients for the two indices, if one takes the sample size information and the number of bleeding sites per treatment group, one can derive the average number of gingival bleeding sites per subject for each treatment group at each examination.

Average Bleeding Sites per Person

	Baseline	3 months	6 months
Fixed Combination of Essential Oils	1068/34 = 31.4	773/34 = 22.7	408/34 = 12.0
Chlorhexidine	1248/36 = 34.7	453/36 = 12.6	386/36 = 10.7
Control	1114/38 = 29.3	747/38 = 19.7	770/37 = 20.8

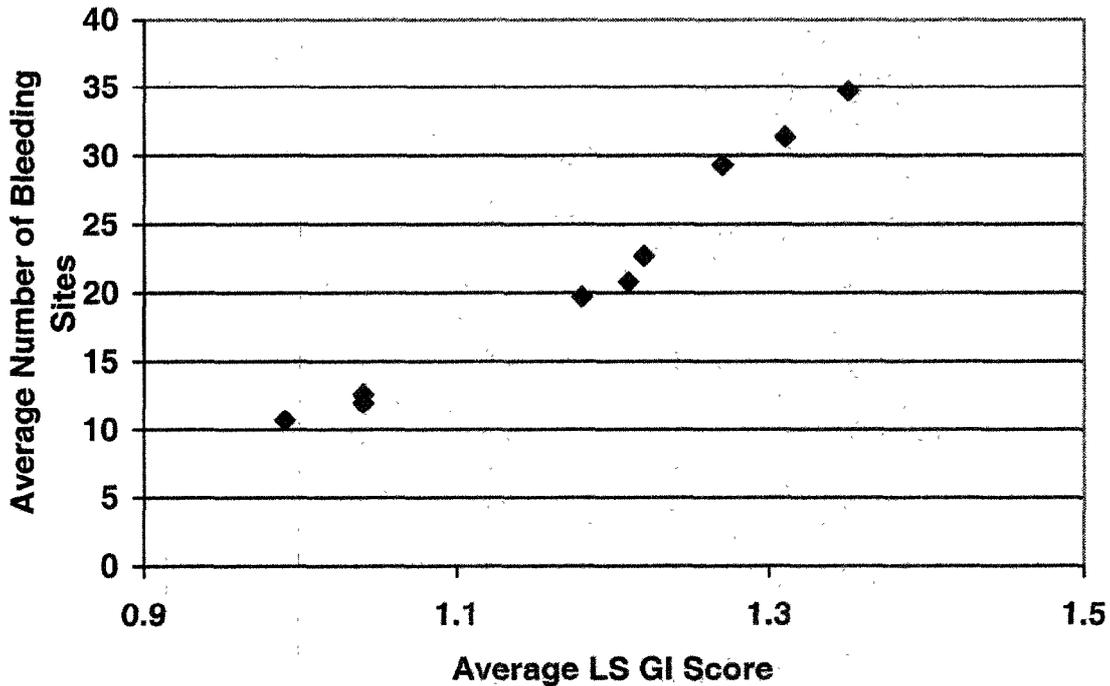
(Data derived from Charles et al., 2004)

¹⁹ CHPA/CTFA Antigingivitis Task Group November 25, 2003 comments to FDA Docket No. 81N-033P, C17, pages 15-22.

²⁰ C.H. Charles, K.M. Mosteler, L.L. Bartels, and S.M. Mankodi (2004) "Comparative Antiplaque and Antigingivitis Effectiveness of a Chlorhexidine and an Essential Oil Mouthrinse: 6-month Clinical Trial", J. Clin. Periodontol, 31:878-884.

The average number of gingival bleeding sites can then be plotted versus the average LS GI score for each of the nine treatment group/examination time combinations.

**Average Number of Bleeding Sites Per Subject
vs. Average LS GI Score**
(Data derived from Charles et al., 2004)



Plotting the average number of bleeding sites versus the average LS GI score results in a linear relationship with an estimated correlation coefficient of 0.980, indicating that the determination of bleeding alone provides a nearly identical assessment of gingivitis as does LS GI score. Perhaps it is not surprising that bleeding and LS GI are so highly correlated considering a change in bleeding can have a numerically greater influence on the overall GI score than a change in visual characteristics. The objective measure of bleeding is arguably a strong indicator of a change in gingival health.

As discussed in the draft guidance, one example of an index by which to assess the severity of gingivitis is the LS GI, which is recognized as a combined index because it incorporates both an objective bleeding component and a more subjective visual component. An alternative index which the Agency has also accepted for assessing

gingivitis²¹, the Modified Gingival Index, is based solely on the subjective assessment of the visual characteristics of gingivitis. Although MGI does not take bleeding into account, the authors of *A Modified Gingival Index for Use in Clinical Trials*²² clearly recognized the importance of bleeding in the clinical assessment of gingivitis:

"...elicitation of bleeding upon pressure may be considered as an advantage of the original GI (i.e. LS GI), in view of the evidence from several groups of workers that bleeding upon pressure or probing may constitute one of the earliest objective signs of gingivitis."

As written, the draft guidance allows for the use of either a combined index which includes bleeding (LS GI) or those indices that rely principally on only the visual characteristics of the disease (MGI). Based on the historical use of these scales, Procter & Gamble is in agreement with recognition of these indices as useful measurement scales for gingivitis. However, Procter & Gamble requests the Agency recognize the importance of bleeding in the assessment of gingivitis and in doing so establish gingival bleeding as a stand-alone primary endpoint. Additionally, we request the Agency consider any or all of the well characterized and validated gingival bleeding assessments as appropriate indices for this stand-alone primary endpoint (e.g. Papilla Bleeding Index⁸; which could actually be considered a combined index, Bleeding Index²³, Sulcus Bleeding Index⁶, Gingival Bleeding Index²⁴, Eastman Interdental Bleeding Index²⁵, etc.).

²¹ Letter 56, Docket 81N-0033P

²² R.R. Lobene, T. Weatherford, N.M. Ross, R.A. Lamm, L. Menaker (1986) "A Modified Gingival Index for Use in Clinical Trials", Clin. Prev. Dent, 8:3-6.

²³ J.E. Mazza, M.G. Newman, and T.N. Sims (1981) "Clinical and Antimicrobial Effect of Stannous Fluoride on Periodontitis", J. Clin. Periodontol, 8:203-212.

²⁴ J. Ainamo and I. Bay (1975) "Problems and proposals for recording gingivitis and plaque", Int. Dent. J, 25:229-35.

²⁵ J.G. Caton and A.M. Polson (1985) "The Interdental Bleeding Index: A Simplified Procedure for Monitoring Gingival Health", Comp. Cont. Edu. Dent, 6:88-92.

2. Standard of care should not confound the results of a clinical trial

The Draft Guidance specifies in Section V.E. that during a chronic clinical study, "subjects should receive the standard of care for gingivitis. This care consists of regular brushing and use of dental floss between professional dental visits to maintain oral health and reduce the incidence and severity of gingivitis." Procter & Gamble agrees and recommends that all individuals should aspire to this standard of care however we are concerned that the current guidance as worded would institute a standard of care in a clinical trial which is well beyond the routine of most subject's oral hygiene practices. The introduction of a new habit at the beginning of a clinical trial can lead to a confounding of the study results. We request that this section be modified to specify that the standard of care should be "regular brushing and continuation of any of their current mechanical oral care habits".

Although regular brushing and flossing constitute the optimal care recommended by dental professionals, actual consumer habits and practices do not reflect this standard. In 1995, Bakdash published a review of 5 independent surveys focused on the patterns and practices of oral hygiene product use in the US²⁶. In that review, approximately 40% of respondents reported using dental floss once or more daily. However, this finding is not supported in a recent report in the ADA News (February 2005) which indicated that 87% of patients floss infrequently or not at all²⁷. Similarly, a national survey conducted in 2003 by McNeil-PPC, Inc., a subsidiary of Johnson & Johnson, reported that only 24 % of U.S. households use floss and only 2.5% of these households floss regularly. An AC Nielsen survey during 2003-2004 suggests that only 33.8% of U.S. households actually had floss. Procter & Gamble's own internal market research data are consistent with these statistics which suggest, unfortunately, that flossing is not a common oral hygiene practice in the United States.

²⁶ B. Bakdash (1995) "Current Patterns of Oral Hygiene Product Use and Practices", *Periodontology* 2000, 8:11-14.

²⁷ K. Fox (2005) "ADA, J&J Join in Floss Campaign" Retrieved October 25, 2005 from ADA News <http://www.ada.org/prof/resources/pubs/adanews/adanewsarticle.asp?articleid=1277>

Clinical trials supporting the efficacy of a number of actives have previously been submitted to the agency through the ongoing review of OTC drug products and recent NDA filings. To the best of our knowledge, the effectiveness of each of these actives, whether monograph or NDA, was demonstrated in the absence of flossing. Importantly the American Dental Association Guidelines for Acceptance of Chemotherapeutic Products were not developed using flossing as the standard of care.

A number of statistical issues are also presented by mandating daily flossing in a clinical study population that does not floss as part of their normal routine. For instance, the introduction of a new oral care habit, like flossing, at the beginning of a clinical trial is likely to result in a substantial Hawthorne effect (a positive change in the performance of a group of persons taking part in an experiment or study due to their perception of being singled out for special consideration), thus significantly reducing the possibility of observing a treatment effect. In addition variation in flossing technique and compliance with a new habit like flossing within a study population will introduce significant variability across the study population further confounding the treatment effect.

Statistical sample size calculations based upon historical data (generated without flossing) would underestimate the true required sample size by an unknown amount. Sponsors would be faced with the prospect of running larger studies than in the past, with increased uncertainty regarding the adequacy of statistical power. Treatment differences that are diminished by an unknown amount (via the Hawthorne effect) combined with variability that is increased by an unknown amount (due to induced behavior differences among subjects) are factors that combine to make statistical planning of clinical studies extremely difficult, if not impossible, if flossing is included in the study design.

Given that the vast majority of the U.S. population does not floss regularly it is particularly relevant to conduct chemotherapeutic gingivitis trials without the introduction of flossing. The introduction of flossing concurrent with a chemotherapeutic treatment will confound the clinical results and compromise the ability to generalize the

effect across an OTC population. Certainly, a clinical participant would not be expected to discontinue the use of floss as a condition of enrollment. For this reason, Procter & Gamble respectfully requests the Agency modify the guidance relative to standard of care (Section V. E.) to read, "regular brushing and continuation of any of their current mechanical oral care habits".

3. Proof of effectiveness should be assessed in a population with a narrow level of disease that can be extrapolated to the general OTC population

Lines 449-451 of the Draft Guidance state that

"... a product intended to be marketed OTC be studied in a population which includes a full range of gingivitis within the indication for non-prescription users to reflect the population that will ultimately use the product."

Procter & Gamble requests that this sentence be modified to read:

"... a product intended to be marketed OTC be studied in a population which is appropriate for determining anti-gingivitis efficacy and for generalizing the efficacy to the population that will ultimately use the product."

This recommendation is consistent with previous conversations between the Agency and Procter & Gamble regarding patient populations for gingivitis clinical trials. Traditionally gingivitis trials have been run in populations with a level of disease sufficient to demonstrate the effectiveness of the drug and within a narrower range of disease which minimizes variability but still allows for the effect to be generalized across the OTC population. Moreover, based on the numerical nature of the accepted gingival indices, including subjects with little or no gingivitis will dilute the treatment effect, making it numerically impossible to achieve the pre-specified reduction threshold established in the draft guidance.

4. Plaque index represents not only a reduction in plaque mass, area, and volume but other assessments of plaque control as well

The Draft Guidance describes various Plaque Index methods to measure the plaque reduction by a chemotherapeutic agent. These indices include the Turesky modification of the Quigley and Hein Plaque Index and the Loe and Silness Plaque Index. Both indices employ a scoring scale corresponding to the amount of plaque identified at a specified number of sites on each tooth. Procter and Gamble believes that use of such plaque indices that measure plaque reductions of mass, area or volume may be insufficient to adequately measure other attributes of plaque control.

We acknowledge that antimicrobial agents effective in the treatment or prevention of gingivitis clearly achieve their therapeutic effect through an antiplaque mechanism. However, it is irrelevant how the antimicrobial agent achieves antigingivitis/antiplaque effectiveness, as long as a clinically-relevant decrease in gingivitis is achieved.

In the preamble to the Advance Notice of Proposed Rulemaking for OTC Antigingivitis/Antiplaque Drugs the Subcommittee stated they accept...

"gingivitis is associated with an accumulation of plaque along the gingival margin but 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."¹⁷

Furthermore the Subcommittee acknowledged that they were unaware...

"of any studies where the volume, mass or amount of plaque can be closely equated with the extent of gingival inflammation."¹⁷

It is Procter & Gamble's position, after review of the literature and our own clinical research, that the bulk of the data supports the concept that plaque-induced gingivitis is an inflammatory condition caused by the indirect effects of dental plaque. Although there is a definite relationship between the presence of dental plaque and gingivitis, it is

the activity of plaque as expressed by the synthesis of metabolic by-products or virulence factors, not the quantity of plaque that promotes the development of gingivitis. These virulence factors implicated in triggering the disease include ammonia²⁸ and lipopolysaccharides^{29,30,31}, a variety of lytic enzymes^{32,33,34} that can damage the epithelium and connective tissue, short chain fatty acids^{35,36,37} that interfere with cellular processes of the host^{38,39}, and presumably many others that have not yet been identified.

²⁸ A. A. Rizzo (1967) "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. Periodontol, 38, 491-499.

²⁹ S. E. Mergenhagen (1960) "Endotoxic Properties of Oral Bacteria as Revealed by the Local Shwartzman Reaction", J. Dent. Res, 32, 267-272.

³⁰ T. Hofstad (1974) "Antibodies Reacting with Lipopolysaccharides from *Bacteroides melaninogenicus*, *Bacteroides fragilis*, and *Fusobacterium nucleatum* in Serum from Normal Human Subjects", J. Infectious Diseases, 129, 349-352.

³¹ T. E. VanDyke and W. B. Zinney (1989) "Biochemical Basis for Control of Plaque-Related Oral Diseases in the Normal and Compromised Host: Periodontal Diseases", J. Dent. Res, 68, 1588-1596.

³² S. Schultz-Haudt, M. A. Bruce and B. G. Bibby (1954) "Bacterial Factors in Nonspecific Gingivitis", J. Dent. Res, 33, 454-458.

³³ P. Soder and G. Frostell (1966) "Proteolytic Activity of Dental Plaque Material. I. Action of Dental Plaque Material on Azocoll, Casein and Gelatin", Acta Odont Scand, 24, 501-515.

³⁴ J. C. Thonard, C. M. Hefflin and A. I. Steinberg (1965) "Neuraminidase Activity in Mixed Culture Supernatant Fluids of Human Oral Bacteria", J. Bacteriology, 89, 924-925.

³⁵ S. S. Socransky, M. Listgarten, C. Hubersak, J. Cotmore and A. Clark (1969) "Morphological and Biochemical Differentiation of Three Types of Small Oral Spirochetes", J. Bacteriology, 98, 878-882.

³⁶ W. J. Loesche and S. S. Socransky (1964) "*Bacteriodes oralis*, Proposed New Species Isolated from the Oral Cavity of Man", J. Bacteriology, 88, 1329-1337.

³⁷ R. E. Montgomery, R. E. Singer, L. D. Ryan, D. W. Leedy, T. W. Keough, A. J. DeStefano (1982) "Relation Between Plaque Butyrate Production and Reversal of Gingivitis", J. Dent. Res, 61, 260.

³⁸ R. E. Singer and B. A. Buckner (1980) "Characterization of Toxic Extracts of In Vitro Cultured Human Plaque", J. Perio. Res, 15, 603-614.

A reduction in the synthesis of these plaque by-products, and therefore a reduction in plaque pathogenicity will manifest itself in a clinically-significant endpoint, i.e., a reduction in gingivitis. For the reasons outlined above, Procter and Gamble requests that the guidance document be modified to expand the description of clinically-meaningful plaque control to include a reduction in plaque mass, virulence, pathogenicity, and/or composition (e.g. a reduction in plaque glycolysis and an inhibition of plaque re-growth (PGRM)⁴⁰, reduction in metabolic factors of specific pathogenic bacteria⁴¹, a decrease in specific pathogenic bacteria, etc.).

³⁹ R. E. Singer and B. A. Buckner (1981) "Butyrate and Propionate: Important Components of Toxic Dental Plaque Extracts", *Infect. Immun.*, 32, 458-463.

⁴⁰ D.J. White, E.R. Cox, N. Liang, D. Macksood, L. Bacca (1995) "A New Plaque Glycolysis and Regrowth Method (PGRM) for the *In Vivo* Determination of Antimicrobial Dentifrice/Rinse Efficacy Towards the Inhibition of Plaque Growth and Metabolism-Method Development, Validation and Initial Activity Screens", *J. Clin. Dent.*, 6 Spec Iss:59-70.

⁴¹ C.J.L. Silwood, E. Lynch, A.W.D. Claxson, M.C. Grootveld (2002) "¹H and ¹³C NMR Spectroscopic Analysis of Human Saliva", *J. Dent. Res.*, 81:422-427.

5. General Comments and Considerations

Ethical Considerations of Conducting a Gingivitis Trial (Section III. F.)

Procter and Gamble agrees with the Agency that the experimental gingivitis model, typically conducted for two or three weeks in duration, has proven to be a valuable tool during the early phases of drug development to determine if a drug product has the potential to be effective. However, we do not agree with the Agency that the use of the experimental gingivitis model may be unethical. The literature supports that any condition induced by the experimental gingivitis model is reversible and that gingival health is restored via a prophylaxis and/or resuming typical oral hygiene^{42,43}. The Agency also implies that experimental gingivitis models were only used "in the past" whereas these models continue to be used today. We therefore recommend the Agency adopt the general position outlined in paragraphs 1 and 2 of section III. F., and omit paragraph 3 altogether.

Blinding (Section V. C.)

The use of a no-treatment study leg or a marketed positive control product may make a double-blind design hard to achieve due to the very distinctive esthetics associated with certain products. Examiner blinding (single blinding), in this case, should be considered appropriate.

Assessment of Gingivitis (Section VII.)

There have been relatively few technological advances in the means of assessing gingivitis and plaque compared to diagnostic advances in most other health-related areas. Procter & Gamble encourages the Agency to support the development of modern technologies to provide more objective and quantitative measures for gingivitis and

⁴² H. Loe, E. Theilade and S.B. Jensen (1965) "Experimental Gingivitis in Man" J. Periodontol, 36:177-187.

⁴³ E. Theilade, W.H. Wright, S. B. Jensen and H. Loe (1966), "Experimental Gingivitis in Man II. A Longitudinal Clinical and Bacteriological Investigation", J. Periodontol Res, 1:1-13.

plaque. In our comments to the ANPRM⁴⁴, Procter & Gamble presented research demonstrating the utility of a unique and sensitive methodology, the Digital Plaque Image Analysis Repeated Measures (DPIARM)⁴⁵ which is a new technology for the objective determination of the ability of a chemotherapeutics agent to remove, prevent or control plaque accumulation on the surfaces of teeth *in vivo*. We request that the draft guidance encourage and promote the continued development of new objective and robust methodologies for the assessment of plaque and gingivitis and provide additional direction (MaPPS) for working with the Agency to evaluate and adopt these new methodologies. Therefore, Procter & Gamble requests that the Agency incorporate the following statement on method development in the guidance document:

“The Agency continues to evaluate new metrics and alternative methods as they are developed for evaluating gingivitis (inflammation and bleeding), plaque etc.”

This statement is analogous to a similar statement that was contained in the Draft Guidance for Industry for Acne Vulgaris (Docket No. 2005D-0340)⁴⁶.

Bleeding on Probing (Section VII. D.)

Bleeding on probing is more commonly used when assessing periodontal break-down and changes at the base of the periodontal pocket, both of which are recognized as secondary endpoints for periodontitis⁴⁷ and not gingivitis. Procter & Gamble respectfully requests that the Agency change the heading of section VII. D. to Bleeding Index, Gingival

⁴⁴ Procter & Gamble's comments to the ANPRM: November 21, 2003 comments to FDA Docket No. 81N-033P, C14 pages 56-62.

⁴⁵ P.A. Sagel, P. G. Lapujade, J. M. Miller, R. J. Sunberg (2000) "Objective Quantification of Plaque Using Digital Image Analysis", *Assesment of Oral Health*, 130-143.

⁴⁶ Federal Register 70(180) September 19, 2005, pages 54945-54946, "Draft Guidance for Industry Acne Vulgaris: Developing Drugs for Treatment", retrieved September 23, 2005, from <http://www.fda.gov/cder/guidance/6499dft.pdf>

⁴⁷ F.N. Hyman, M.E. Welch, J.R. Cheever (1997) "Regulatory Issues for Evaluation of Therapies to Prevent or Arrest Disease Progression", *Ann. Periodontol*, 2:166-179.

Bleeding Index or some other term that more accurately describes the evaluation being made.

The last sentence of this section states:

“Automated periodontal probes may improve the accuracy and precision of probing depth measurements.”

Gingival indices do not require probing depth measurements and automated probes are not used for supragingival measurements associated with gingivitis. Procter & Gamble respectfully requests that the Agency delete this sentence.

Section VII. E-G.

Under the section entitled Assessment of Gingivitis the Agency has described several non-therapeutic endpoints such as calculus, stain, and microbiology. The inclusion of these measures in this section could potentially cause confusion. Although we do not believe it is the intent of the Agency to suggest that these are either therapeutic endpoints or assessments that need to be made during the course of a pivotal gingivitis clinical trial, we do believe that this could be a possible interpretation. Therefore, Procter & Gamble requests the Agency clarify that the evaluation of non-therapeutic endpoints does not need to be conducted in conjunction with a pivotal gingivitis trial.

Clinical Significance (Section VIII. A.)

The draft guidance recommends that the approval of an antigingivitis drug should depend on the sponsor demonstrating the drug has an arithmetic mean of the estimated proportionate reductions for the GI measurement in at least two studies and be no less than 20 percent, consistent with the criteria outlined by Imrey et al.⁴⁸ Procter & Gamble is on record stating “the reliance on a minimum percent difference between treatments is

⁴⁸ P.B. Imrey, N.W. Chilton, B.L. Pihlstrom, H.M. Proskin, A. Kingman, M.A. Listgarten, S.O. Zimmerman, S.G. Ciancio, M.E. Cohen, R.B. D’Agostino, S.L. Fischman, J.L. Fleiss, J.C. Gunsolley, R.L. Kent, W.J. Killoy, L.L. Laster, R.G. Marks, and A.O. Varma (1994) “Recommended Revisions to American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for Gingivitis Control”, J. Periodontol, 29:299-304.

insufficient for an adequate judgment of clinical significance^{15,44}. However, based on the continued use of the threshold for the combined index, LS GI, for which the threshold was originally established and subsequently applied to the visual characteristic only index, MGI, Procter & Gamble requests that the Agency apply the same threshold to all stand-alone primary endpoints including the Gingival Bleeding Index.

Statistical Considerations (Section VIII. B.)

The third paragraph of this section describes bleeding upon probing as a site-specific dichotomous variable where "*a repeated measures approach may be appropriate.*" Current standard practice in industry and in the gingivitis clinical literature is to summarize bleeding site data on a per-subject basis either by the total number of bleeding sites in the mouth or by the proportion of sites with bleeding (of the total number of sites examined in the mouth). These variables are then subjected to analysis of covariance methodology in a similar fashion to the GI and PI (with possible mathematical transformations applied). Therefore, Procter & Gamble requests that this standard statistical practice be included in the guidelines regarding the analysis of bleeding data.

Procter & Gamble asks that the Agency give careful consideration to these comments and if we can be of further assistance please don't hesitate to contact us.

Respectfully submitted on behalf of The Procter & Gamble Company



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