



5.E. Clinical significance in gingivitis trials should be based on a 15% reduction in gingivitis, which is the level of improvement achievable by consumers in home-based oral hygiene interventions

During the call-for-data, sponsors submitted data to the Plaque Subcommittee to establish the safety and effectiveness of active ingredients with antiplaque and/or antigingivitis activity. Because there were no specific FDA guidelines regarding the type or level of effect that needed to be demonstrated to establish antigingivitis effectiveness, the Plaque Subcommittee used a weight of evidence approach in their determination of effectiveness for each active ingredient. Although this approach was very thoughtful and rigorous, the process is not logistically reasonable to use as the rulemaking process moves forward. Companies need to have established criterion to determine clinical significance for their products. There are several situations under this rulemaking process where the necessity for such clinical significance criteria would be useful:

1. Upgrading a Category III(E) ingredient to Category I
2. Conducting a 6-month study to confirm the effectiveness of an alternate dose form
3. Conducting a study on a new combination product
4. Consideration of an antigingivitis/antiplaque agent marketed in a foreign country for inclusion in the US monograph.

The discussion to follow discusses reviews of the literature in regards to the level of improvement that is achievable by consumers in a conscientiously applied home-based oral hygiene program. In two independent studies of consumers who self-reported their oral hygiene habits, and whose oral hygiene was graded by a dental professional, approximately a 15% improvement (reduction) in gingivitis was observed when home-

based oral hygiene habits (brushing/flossing) were applied. In contrast, when professional-based interventions were measured, a larger 20% gingivitis reduction was observed. Therefore, for an OTC product to be marketed under the monograph, it is appropriate to conclude that the level of improvement achievable from home-based oral hygiene should be the same as the level of gingivitis improvement needed for an OTC product in a 6-month gingivitis trial. Thus, we recommend that a 15% gingivitis reduction be established as the minimum level needed for clinical significance under the monograph.

5.E.1. The Agency needs to consider a framework in which to judge the clinical significance of results of a gingivitis clinical trial.

This framework would be applicable to all clinical studies to establish

- Clinical efficacy of a Category I active ingredient formulated in a dosage form other than the reviewed dosage form
- Clinical efficacy of a Category III active ingredient to support reclassification to Category I status
- Clinical efficacy of a final formulation, if and when a manufacturer chooses to demonstrate bioequivalence by this means rather than through the bioequivalence approach outlined above

In judging the results of a clinical trial, it is critical to have a framework in which it is possible to assess the clinical significance of those results. While a particular therapy may achieve statistical significance over a control in a randomized, controlled study, it is of little practical value without also providing a result that is of meaning to the consumer and the professional.

In most gingivitis clinical studies, results are reported as a % reduction of specific symptoms (inflammation, bleeding) for subjects in the test treatment group relative to subjects receiving a control after defined periods of time (typically 6 months). Currently, the established guidelines of the American Dental Association require a treatment provide an average minimum 20% reduction in gingivitis across studies in order to gain its Seal of Acceptance. In its deliberations to make recommendations for the OTC monograph, the Plaque Subcommittee strongly encouraged sponsors of submissions to explore alternative ways to evaluate the clinical significance of results from gingivitis clinical trials as the Subcommittee did not believe a simple proportionate difference was adequate for their task. To this end, several additional methods of analysis were developed and presented to the Subcommittee. The results of these analysis methods were subsequently utilized by the Subcommittee to recommend stannous fluoride, cetylpyridinium chloride and essential oils as category 1 actives.

5.E.2. “Weight of the Evidence” Analysis Utilized by the Plaque Subcommittee

5.E.2.1. Statistically significant reductions in gingivitis.

Obviously, the first and foremost criterion is that results from randomized trials show a statistically significant reduction in gingivitis for the active under consideration relative to its control in a 6-month study. However, the Subcommittee strongly urged manufacturer’s of drug products to develop additional approaches to allow for a more thorough assessment of anti-gingivitis efficacy.

5.E.2.2. Site-Specific Analyses

While it is recognized that the correct statistical unit of observation is the subject, much can be ascertained regarding the anti-gingivitis effects of chemotherapeutic agents by considering the fate of individual sites within the oral cavity, particularly since the Löe-Silness index conveniently assesses gingivitis at up to 168 individual sites surrounding the dentition. Two distinct site-specific analyses provide insight regarding clinical significance. The first is a natural extension of a typical % reduction analysis and provides information on the degree to which the overall % reduction is a function of prevention and/or treatment. In this analysis, gingival bleeding is considered more clinically relevant than redness. For each subject at baseline, sites are categorized into bleeding and non-bleeding, based on the Löe-Silness examination. Considering only those sites initially bleeding, the degree to which the chemotherapeutic agent converts these to non-bleeding (relative to the control) is a measure of treatment of gingivitis. Likewise, considering only those sites initially non-bleeding, the degree to which the chemotherapeutic agent maintains these as non-bleeding (relative to the control) is a measure of prevention of gingivitis. (Combined, these outcomes constitute the overall % reduction in gingival bleeding the test treatment achieves in the clinical trial.)

A second site-specific analysis addresses the degree to which a chemotherapeutic agent affords improvements in oral health throughout the gingival tissue by providing information on the site distribution of effectiveness. To do so, the average response at a given site is computed by averaging the Löe-Silness scores for that site from all subjects in a particular treatment group at the end of a clinical study. By comparing the test and control treatments, it is possible to determine the extent to which a chemotherapeutic agent provides its benefit across the dentition. Further, since certain sites are more prone to gingivitis than others, this analysis provides insight into whether or not the active agent is effective at these more susceptible sites. For an effective treatment, it is expected that there will be less gingivitis at the majority of sites in subjects using the test product relative to the control.

I. Subject-based Analysis

Subject-based analysis provides another approach to assess the clinical significance of a test agent's treatment effect. This analysis involves comparing gingival health at baseline versus that observed after some treatment period for individual subjects receiving a test treatment or a control. To perform this analysis, the improvement in overall gingival health from baseline is computed for each subject in a given treatment group. Since each subject typically responds somewhat differently, the distribution in improvement for the active group is compared to that of the control group. For an active agent, it will be observed that a greater % of subjects will achieve a larger improvement in gingival health than subjects randomized to the control group.

II. Improvements Relative to Oral Hygiene Habits

One approach to judging clinical significance is to compare the improvements in gingival health that are obtained after using a test agent for 6 months (relative to control) to those improvements that might be reasonably achieved from enhanced oral hygiene habits. To provide a basis for this analysis, it is necessary to have (from an independent study) information relating levels of gingivitis and gingival bleeding to self-reported oral hygiene practices, particularly brushing frequency, flossing frequency and frequency of regular dental visits. From such data, it is possible to compute the likely improvement in gingival health that would occur if an individual were to improve his/her oral hygiene. This approach, of comparing to putative effects of improved oral habits, is particularly fruitful in that it is generally recognized and accepted that increases in brushing, flossing or dental visit frequencies will result in clinically significant improvements to gingival health and thus represents a rather non-controversial approach to judging the significance of results of clinical trials.

III. Odds Ratios Analyses

As a last approach to judging clinical significance, odds ratios analyses were performed. In this approach, the odds of a subject achieving a meaningful improvement in gingival bleeding (defined as at least 50% reduction) from baseline were calculated for subjects in the test group and again for those in the control group. From these, the odds ratios were computed. An odds ratio of 1.0 indicates subjects are just as likely to achieve the improvement in gingival bleeding on the test treatment as on the control while an odds ratio greater than 1.0 indicates subjects in the active treatment group are more likely to receive the benefit than those in the control group. Further, it is possible to perform a meta-analysis of odds ratios from multiple studies investigating the effects of a given treatment; from this approach, information from all pooled studies can be brought to bear on the question of clinical significance.

5.E.3. The “Weight of the Evidence” Analysis Utilized by the Plaque Subcommittee Is Not Appropriate for a Monograph

Collectively, these approaches to judging clinical significance were utilized in an effort to provide a more insightful and thorough assessment than relying on a simple % reduction analysis. In the end, these types of analyses were conducted on trials for stannous fluoride, cetylpyridinium chloride and essential oils and the Subcommittee made a ‘weight-of-the-evidence’ judgment. However, the Subcommittee agreed upon no specific, quantitative criteria as to what constituted a clinically significant reduction in gingivitis. As such, it will be difficult to rely on these types of analyses for judging results from future clinical trials (such as may be submitted for actives that are currently recommended by the Subcommittee as Category 3 or for trials submitted for Category 1 actives in alternative dosage forms).

5.E.4. The Proportional Reduction Analysis Is Appropriate for Inclusion In The Monograph

5.E.4.1 P&G Recommends Inclusion of The Proportional Reduction Analysis Into The Monograph

A proportional reduction analysis is recommended for inclusion in the monograph. A statistically significant 15% reduction in gingivitis must be achieved in a 6-month clinical trial for that active or dosage form to be considered as providing a meaningful level of improvement in health. The basis of this criterion is that 15% represents that level of improvement achievable by consumers in home-based oral hygiene interventions.

In an effort to provide specific, easily applied criteria, the following is offered. The obvious starting point is to consider relying on the current ADA criteria. These utilize a simple proportionate analysis and require at least a 15% reduction in gingivitis for the active relative to control from any one trial and, furthermore, the average reductions across at least 2 trials are no less than 20%. In all trials, statistical significance is required as well. Reliance on these criteria per se, however, is not appropriate for the task at hand. It must be recognized that the ADA Seal of Acceptance is, in essence, a communal recommendation by the dental profession of a drug product's effectiveness; the focus of the monograph process is drug active, not product. Further, monograph drug actives are typically recommended at a minimally effective dose to ensure safe use by a broad population while maintaining a reasonable expectation of effectiveness. The objective of the Seal program is distinctly different from that of determining what active and corresponding dosage forms have sufficient anti-gingivitis efficacy to be included in the proposed FDA Plaque/Gingivitis monograph. In fact, in developing the ADA guidelines, the Task Force on Design and Analysis (commissioned by ADA to recommend revisions to their guidelines) specifically stated, "In this connection, the obligations of the ADA and the Food and

Drug Administration are by no means identical.”⁷⁷ Thus, the approach of the ADA guidelines (proportionate analysis) is simple to apply but their specific criteria are not appropriate to the needs of the monograph.

One may go further and ask if there is a level of reduction (expressed as a % difference from control since this approach is easily utilized) that is appropriate for the monograph. To this end, it may be argued that a drug active that provides a level of benefit that is comparable to that derived from improved consumer-based oral hygiene measures that are readily available and universally recommended by the dental profession would be providing a clinically meaningful benefit.

During the Plaque Subcommittee deliberations, results from a cross-sectional survey study conducted by Procter & Gamble were presented. Essentially, this study involved measuring gingivitis from almost 1000 consumers while simultaneously asking these individuals a series of questions regarding their current oral hygiene habits. From these data, one may categorize individuals according to their reported oral hygiene habits and determine if there are differences in gingivitis. This was in fact done, and the results of this survey are presented here:

Subjects reporting:	Had less gingivitis:	Than subjects reporting:
Brush teeth 2x/day	17%	Brush teeth 1x/day
Never floss	11%	Floss but < 1x/week
Floss but < 1x/week	12%	Floss 1/week
Floss 1/week	15%	Floss 1/day
Average change	14%	

From this study, the average improvement in gingivitis for a step change in consumer-based oral hygiene was approximately 14%.

⁷⁷ J Periodont Res 1994, 29: 299-304.

In an independent study, Lang examined 397 adults from the Detroit MI area for gingivitis and simultaneously queried them for their self-reported oral hygiene habits.⁷⁸ His results are similar to those above:

Subjects reporting:	Had less gingivitis:	Than subjects reporting:
Acceptable brushing	17.5%	Not acceptable brushing
Acceptable flossing	15.5%	Not acceptable flossing
Average change	17%	

In his study, acceptable brushing and flossing were defined as at least brushing/flossing at least once per day.

Considering these two trials collectively, one may argue that a meaningful change in home-based oral hygiene measures results in approximately 15% less gingivitis. This may then be taken as that level of improvement needed for an active (or an active in an alternative dosage form) to be considered for inclusion into the monograph. The fact that this level of efficacy is less than that required by ADA for their Seal program is appropriate, given the different objectives of these guidelines from that of the monograph.

As a check of internal consistency, one may naturally assume that professional-based interventions in gingivitis should result in greater improvements in health than home-based measures. The above two survey studies also assessed the frequency with which consumers received regular, routine dental cleanings. These results were:

⁷⁸ J Clin Periodontol 1994, 21, 194-8 and J Public Health Dent 1995, 55, 10-17

Subjects reporting:	Had less gingivitis:	Than subjects reporting:
Visit dentist < 1/year	14%	Visit dentist 1/year
Visit dentist 1/year	19%	Visit dentist 2/year
Acceptable frequency of dental check up (at least once per year)	28.4%	Not acceptable frequency of dental check up

Thus, across these two studies, more frequent professional intervention resulted in approximately 20% reductions in gingivitis.

A final piece of clinical data is relevant to this discussion. In a prospective clinical trial, the % reduction in gingivitis resulting from a dental prophylaxis was measured (J Periodontol 2001, 72, 383-92). Approximately 300 subjects were randomly assigned to receive a dental prophy or not and the improvement in gingivitis was measured by multiple clinicians. The average improvement was 20% as shown by the data below:

Clinician	% Reduction for Prophylaxis		Clinician	% Reduction for Prophylaxis
1	15.3		7	25.7
2	17.9		8	13.8
3	9.4		9	20.1
4	22.7		10	26.3
5	22.7		11	39.3
6	15.4		12	14.0

A proportional reduction analysis is recommended for inclusion in the monograph. A statistically significant 15% reduction in gingivitis must be achieved in a 6-month clinical trial for that active or dosage form to be considered as providing a meaningful level of improvement in health. The basis of this criterion is that 15% represents that level of improvement achievable by consumers in home-based oral hygiene interventions.

5.E.5 Future Research Is Needed For Other Methods To Be Included In The Monograph

A simple % difference between active and control is easy to apply to the results of a given trial. However, when comparing across studies, a proportionate analysis is not optimal. There are many variables that contribute to the observed % difference which are difficult to control for across studies, particularly trials conducted by different research organizations. To this end, inclusion of an internal standard may offer some advantages. As noted above, it is possible to measure the reduction in gingivitis from a dental prophylaxis. Since many gingivitis clinical trials use designs that include a dental prophylaxis immediately following baseline examinations and before any test product usage, it may be feasible to measure the reduction in inflammation and bleeding from the dental cleaning and use this as an internal study standard. Research in this area has only recently begun and as a consequence, it is premature to attempt to utilize this approach for the monograph at this time. Nonetheless, future change may be warranted.

We ask that the Agency give careful consideration to these comments. If Procter & Gamble can be of further assistance, please do not hesitate to contact:

Respectfully submitted on behalf of The Procter & Gamble Company


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Appendices

1. .“Proposed PGRM Test and Effectiveness Criteria for Performance Evaluation of Formulations Containing Antiplaque/Antigingivitis agents, Stannous Fluoride & Cetylpyridinium Chloride – Additional Considerations,” Procter & Gamble Research Report
2. Method to Determine ‘Bioavailable Cetylpyridinium Chloride’ in Mouthrinses by an *In Vitro* Disk Retention Assay,” Procter & Gamble Research Report.
3. Mankodi, S. et. al.: Clinical Efficacy of an Optimized Stannous Fluoride Dentifrice, Part 2: A 6-Month Plaque/Gingivitis Clinical Study, Northeast USA, Compendium (Special Issue); 18: pp10-15, 1997.
4. Williams C. et. al., Clinical Efficacy of an Optimized Stannous Fluoride Dentifrice, Part 3: A 6-Month Plaque/Gingivitis Clinical Study, Southeast USA, Compendium (Special Issue); 18: pp16-20, 1997.
5. “A Clinical Study to Assess the Antigingivitis Efficacy of a Stannous Fluoride Dentifrice” (Procter& Gamble’s Research Report), unpublished study.
6. “Evaluation of Experimental Dentifrice Formulations for Reducing Plaque and Gingivitis Using the Toothshield Clinical Model” (Procter & Gamble’s Research Report), unpublished study.
7. “Digital Plaque Imaging Analysis Repeated Measures (DPIARM) – A study of Two Stannous Fluoride Dentifrices” (Procter & Gamble’s Research Report), unpublished study.
8. “HBA-CPC and Stannous Fluoride Time Kill Study” (Procter & Gamble’s Research Report), unpublished study.
9. “Minimum Inhibitory Dilution (MID) and Minimum Bactericidal Dilution (MBD) Analysis of High Bioavailable CPC Rinse Formulation Against Organisms Implicated in Gingivitis” (Procter & Gamble’s Research Report), unpublished study.

10. "Oral Biofilm Inhibiting Properties of CPC and Stannous Fluoride," (Procter & Gamble Research Report), unpublished study.
11. "Live/Dead Staining of *In Vitro* CPC and Stannous Treated Saliva Samples," (Procter & Gamble Research Report), unpublished study.
12. Ramji, N. and J. Barnes, "Antimicrobial Efficacy of High-Bioavailable Cetylpyridinium Chloride Rinse," (Procter & Gamble's Research Report), unpublished study.