

Acceptance Program Guidelines

Adjunctive Dental Therapies for the Reduction of Plaque and Gingivitis



American Dental Association

Council on Scientific Affairs September 1997

Council on Scientific Affairs
Adjunctive Dental Therapies for
the Reduction of Plaque and Gingivitis

Scope:

These guidelines apply to the design of clinical trials to evaluate the safety and effectiveness of adjunctive devices, products, or systems intended for the mechanical removal of dental plaque and reduction of gingivitis. Products which contain chemotherapeutic agents must comply with the ADA Acceptance Program Guidelines for Chemotherapeutic Products for Control of Gingivitis or Chemotherapeutic Agents to Slow or Arrest Periodontitis.

I. SUBMISSION DIRECTIONS

1. General Information

- A Submissions are to be sent to the Council Office:
Director, Product Evaluations
Council on Scientific Affairs
American Dental Association
211 East Chicago Avenue
Chicago, Illinois 60611-2678
- B Submissions are to be sent in triplicate along with a market sample of the product, i.e., packaged as marketed. The Council agrees to return the product sample within 6 months if requested. If possible, the submission should be less than 200 pages exclusive of appendices.
- C A manufacturer is advised that the review process is complex. Typically, notification of Council action may be expected 90 to 150 days from the receipt of a complete submission by the Council. More time may be required if additional information or clarification is needed from the manufacturer.
- D When a product is classified as "Accepted" the classification is for 3 years. Renewal of the classification will be considered by the Council upon request by the manufacturer.
- E Companies with Accepted products are subject to the conditions stated in the Agreement Governing Use of ADA Seal of Acceptance.

2. Arrangement of a Submission

- A The submission is to be divided into sections and arranged in order as indicated in part II. Sections to be identified by tabs are designated by an asterisk (*).

II. INFORMATION TO BE SUBMITTED

1. **Cover Page**

- A Name of company
- B Product name

*2. **Table of Contents**

*3. **Company Information**

- A Name of company (to be used in official list of Accepted Products)
- B Address (to be used in listing)
- C Phone number (to be used in listing)
- D Fax number
- E Names of owners, officers and other individuals authorized to furnish information to the Council and represent the firm in dealing with the Council, including the main contact person. (Foreign manufacturers must have an office or branch located in the United States and the product must be available for purchase in the United States.)
- F Names and qualifications of scientific personnel responsible for formulation and testing of the product in its manufacturing process.

*4. **Summary of Submission**

Comprehensive summary of the information submitted on safety and effectiveness.

*5. **Product Information**

- A Name of product (to be used in listing)
- B Claims of efficacy
 - (i) Claims for the product in labeling and in advertising to the public shall be limited to those related to the use of adjunctive methods or devices for the reduction of plaque and gingivitis above that achieved by normal oral hygiene procedures.
 - (ii) All claims of efficacy, including all health benefit claims and all claims which imply a health benefit (e.g., reduction in gingival inflammation), must be documented. These claims include "reduces gingivitis," "reduces gingival bleeding," "reduces risk of periodontal destruction," "reduces risk of attachment loss," and "reduces risk of tooth loss."
 - (iii) Advertisements must avoid disparagement of other products.

- (iv) The Council believes that because plaque is the etiologic agent for gingivitis, the only Accepted products that will be allowed to make plaque control or plaque modification claims will be those that can demonstrate a significant effect against gingivitis. If a product can only demonstrate plaque reduction without a concomitant significant reduction in gingivitis, it will not be eligible for Acceptance.
- (v) Council consideration of the product is simplified if claims for the product are limited to those noted in section (i). If the claims for the submitted product exceed those claims specified above (e.g., gingival health benefits), it will be necessary to provide adequate evidence of the claimed usefulness of the product. This evidence may be in the form of published reports or unpublished information obtained from appropriate scientific studies employing laboratory, animal, and clinical observations.

- c Patent title(s) and patent number(s) relating to the product
- d Product description
 - (i) List the materials used in the construction of the product
 - (ii) Principles of design
- e Instructions including indications and contraindications for use, warnings, limitations, etc.
- f Labeling/packaging
- g Promotional materials. (Promotional materials need not be developed prior to submission of the product, however, all promotional materials must be approved by the Council prior to use.)

***6. Quality Control Procedures for Manufacturing of the Product**

This should include the quality control tests used during processing and on the finished product, and assurance that the product meets good manufacturing procedures.

***7. Efficacy Data** (clinical data to show effectiveness)

Product efficacy must be demonstrated by two independent, well-designed, clinical studies (minimum 4 weeks) utilizing a control and conducted by independent investigators. All published studies showing the effectiveness of the product must be referenced, including studies that do not show any effect. All proprietary studies, including those that do not show any effect, must also be provided.

Studies should assess the ability of the test product to reduce gingivitis and, to inhibit or reduce plaque formation or plaque pathogenicity. Masked studies are required. At least one study should be conducted on a US population. Populations selected for the studies must be representative of individuals for whom the product is intended, which, in most cases, would be individuals with mild to moderate gingivitis. Trials must report all treatment groups.

- A Statistically significant reductions in both the clinical manifestations of gingivitis and the inhibition of or reduction of plaque or plaque pathogenicity should be demonstrated. Reductions relative to plaque and gingivitis should be demonstrated in two studies and be measured against a placebo control rather than baseline scores. The product must show clinical significance in gingivitis reduction compared to placebo controls in at least two clinical studies.

- B Gingivitis measurements shall demonstrate:
 - (i) that the estimated proportionate reductions [i.e., (control–active)/control] be no less than 15% in favor of the active treatment with a confidence interval of $\pm 10\%$, and statistically significant in each of at least two studies;
 - (ii) that, in addition, the arithmetic mean of the estimated proportionate reductions [i.e., (control–active)/control] across the above studies be no less than 20%. For example, two studies exhibiting statistically significant reductions of 20% or more in both indices would meet these criteria, as would two studies with respective statistically significant reductions of 27% and 15% for the selected bleeding index and 17% and 24% for the Löe–Silness GI. “Proportionate reduction” above refers to a comparison of the active therapy to the control at the end of the study, rather than to reductions from an initial baseline level, and presumes that randomization has produced initially comparable active and control clinical samples, or that fully appropriate statistical adjustment has been used for randomization failures.

- C Plaque measurements shall demonstrate that quantitative plaque reductions or reductions in plaque pathogenicity are statistically significant for those products whose anti-gingivitis action is through plaque reduction or modification.

- D If the mechanism(s) of action is known, supporting data should be provided.

***8. Safety Data**

- A Evidence must be provided that the components of the product are safe for use in the oral cavity. Compliance with applicable FDA standards should be provided (where appropriate).

- B Adequate evidence must be provided from at least two clinical investigations to show that unsupervised use of the product by the average patient will not be harmful to hard or soft tissues, or restorations.

- C For products which contain antimicrobial agents as part of their active ingredients, it must be demonstrated that pathogenic or opportunistic microorganisms do not develop over the course of the study.

- D For products which contain active chemotherapeutic agents, information must be submitted regarding possible toxic effects of the active product and its formulation. In most cases, standard toxicological profiles are sufficient.

***9. Comprehensive Bibliography Concerning the Product**

***10. Copies of Most Significant Articles**

***11. Appendices**

Detailed description of test evaluation methods and any other defined areas

III. STATEMENT TO BE USED FOR PRODUCTS CLASSIFIED UNDER THESE GUIDELINES INCLUDING QUALIFIERS

There will be two Seal statements to be used with an Accepted product, depending on whether or not its mechanism of action is related to plaque reduction.

Statement 1: For Both Gingivitis and Plaque Reduction

"[Product Name] has been shown to be an effective adjunctive product for the reduction of supragingival plaque and gingivitis when used as directed in conjunction with a conscientiously applied program of oral hygiene and regular professional care. Its effect on periodontitis has not been determined." Council on Scientific Affairs, ADA.

Statement 2: For Gingivitis Reduction Only

"[Product Name] has been shown to be an effective adjunctive product for the reduction of gingivitis when used as directed in conjunction with a conscientiously applied program of oral hygiene and regular professional care. Its effect on periodontitis has not been determined." Council on Scientific Affairs, ADA.

IV. REFERENCES FOR FURTHER EXPLANATION

The following references were used in the development of these guidelines. They can be consulted for a more detailed discussion of issues addressed in these guidelines.

- A Council on Dental Therapeutics Guidelines for Acceptance of Chemotherapeutic Products for the Control of Supragingival Plaque and Gingivitis. *J Am Dent Assoc* 1986; 112:529–532.
- B Recommended Revisions to American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for Gingivitis Control. *J Periodont Res* 1994; 29:299–304.
- C Council on Scientific Affairs, Guidelines for Acceptance of Chemotherapeutic Products for Control of Gingivitis, 1997.
- D Council on Scientific Affairs, Guidelines for Acceptance of Dental Floss and Other Interdental Cleaners, 1997.

APPENDIX

SAMPLE CLINICAL PROTOCOL

The following protocol is only one possible design to demonstrate safety and effectiveness of adjunctive dental therapies for the reduction of plaque and gingivitis when used in conjunction with standard oral hygiene procedures. Other well-controlled study designs following similar procedures may be acceptable. Manufacturers are invited to submit protocols for review before implementing a study. If the product is intended to replace or act as a substitute for a component of standard oral hygiene practices (e.g., interproximal plaque removal), the study design must reflect this.

Study Design

Patient Population:

Control subjects will be randomly assigned a commercially available ADA Accepted toothbrush and dental floss (if applicable), test subjects will be randomly assigned the test product and the same ADA Accepted oral hygiene devices. If the test product contains a chemotherapeutic active ingredient (e.g., antimicrobial), a placebo-controlled group will be required. Sufficient subjects shall be enrolled in the study so that a statistically significant difference between the active and control groups can be demonstrated. Control and test subjects should be homogeneous with respect to disease severity (e.g., all with similar levels of gingivitis).

A sufficient number of study sites in each patient should be examined during the study to determine the effectiveness of the adjunctive product for teeth in anterior/posterior and maxillary/mandibular areas of the mouth.

Study Protocol:

Each subject will have a complete examination of the oral cavity to determine eligibility for the study. In general, subjects should be adults in good medical health with mouths free from major hard or soft tissue lesions.

All clinical examinations will be performed by an investigator who has no knowledge of the oral hygiene devices used by the subjects. Clinical measurements will be taken at baseline (prior to the study), at 15 days and at the end of the study (4 weeks).

At the baseline visit, patients will be given written and verbal oral hygiene instructions consistent with proposed claims for the product, (e.g., if claims address effectiveness compared to brushing and flossing), then both brushing and flossing instructions must be given. If the adjunctive device is intended to replace standard interproximal care, patients in the Test Product Group (ADA Accepted toothbrush + test product) will not be given instructions for interproximal care. Instructions will be given by an investigator other than the clinical examiner.

Safety assessments will be made at each measurement visit. Areas to be examined will be tongue, hard and soft palate, hard tissue, dental restorations, gingivae, mucobuccal folds, the inner surface of the cheeks, and sublingual space areas. All areas will be assessed and reported as normal or abnormal, per patient. Evaluations will be performed by a trained investigator.

At each visit, scoring of supragingival plaque will be done at all study sites using an acceptable plaque-scoring system. One of the acceptable systems is the Turesky modification of the Quigley–Hein plaque index¹. Other suitable plaque indices may also be acceptable. The index used, the rationale for its use, and any modification in the method of using it should be clearly explained. Separate plaque scores will be given for the interproximal papillae and gingival margins for both buccal/lingual and mesial/distal surfaces.

At each visit, scoring of gingival inflammation (gingivitis) will be done at all study sites. The Gingival Index of Loe & Silness² is an acceptable method. If a different index is used, its rationale should be provided. Additional assessments of interproximal health such as bleeding on probing are recommended. Assessment of gingivitis should be done prior to the scoring of plaque to avoid masking the gingival inflammation with plaque-disclosing agents.

Between the baseline and 4-week examination, each subject will be instructed to clean his/her teeth twice daily, using only the assigned products provided and a dentifrice provided. During the study, subjects should not use antimicrobial mouthrinses or other dental products that might affect plaque or gingivitis scores.

Compliance should be assessed by appropriate methods (e.g., patient-recorded oral hygiene logs). As an aid to establish compliance, toothbrushes and, if applicable, unused floss (or the test interproximal cleaning product/device) should be returned at the end of the study.

Data analysis:

Within each group, means and standard deviations will be calculated for all clinical measurements and assessments for the entire dentition of each subject, for specific selected sites (e.g., buccal/lingual interproximals), and anterior/posterior teeth. Percent reductions in plaque scores will be calculated by comparing pre- and post-oral hygiene values. Repeated measures multivariate analyses of variance (ANOVA) can be used to test for time- and device-dependent differences for all clinical assessments between the subject groups over the 3 visits. The effects of the oral hygiene devices in reducing baseline values of the plaque and gingivitis indices at the 15-day and 30-day visits can be assessed using the Wilcoxon signed ranks test. Other acceptable methods of statistical analysis are possible.

Safety Reporting:

All adverse events (e.g., tissue irritation) whether reported by the patient or noted by the investigator will be recorded on an appropriate case report form. The investigator(s) will record opinions of the relationship of the study products to each adverse reaction or change in the oral cavity. Any serious adverse experience will be reported to appropriate regulatory agencies. Safety evaluation data (normal vs abnormal) will be analyzed by an acceptable non-parametric statistical test.

References

1. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of Vitamin C. *J Periodontol* 1970; 41:41–43.
2. Loe H, Silness J. Periodontal disease in pregnancy. I. Prevalence and severity. *Acta Odontol Scand* 1963; 21:533–551.

