

## Acceptance Program Guidelines

# Chemotherapeutic Agents to Slow, Arrest or Reverse Periodontitis

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**ADA** American  
Dental  
Association®  
Council on  
Scientific Affairs

2010



Council on Scientific Affairs

## Chemotherapeutic Agents to Slow, Arrest or Reverse Periodontitis

Scope:

These guidelines apply to products used to slow, arrest or reverse periodontitis. The periodontal diseases represent a wide array of infections characterized by variable microbial clusters and host susceptibility factors that may require different therapeutic approaches.

There are two basic ways to control periodontitis:

1. Target the putative microbial components with anti-infective strategies;
2. Strengthen or suppress the host response with host modulation agents.

Products that are designed for the prevention and/or control of gingivitis are addressed elsewhere and are not considered in these guidelines.

## 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 E. Chicago Avenue  
Chicago, IL 60611-2678
- B Submissions are to be sent in triplicate, along with one single-sided copy for duplicating purposes. Three samples of each product from different lots shall be provided. Market samples are preferred. 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-mail address
  - 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.
4. Summary of Submission

Comprehensive summary of the information submitted and safety and effectiveness of therapeutic products used for the control of periodontitis.
5. Product Information
  - A Name of product
  - B Claims of efficacy
    - (i) Improvement in clinical signs of periodontitis must be documented (see below). These claims include, but are not limited to, "gain in periodontal attachment," "improved bone height," and "rebuilding lost bone."
    - (ii) Advertisements must avoid disparagement of other treatments and/or products.
    - (iii) The only Accepted products that will be allowed to make claims of control of periodontitis will be those that can demonstrate: a) the ability to slow the progression of disease, b) the ability to arrest disease progression or c) the ability to reverse the effects of periodontitis.
  - C Patent title(s) and patent number(s) relating to the product.
  - D Product description

(i) Chemical composition and amounts

E Instructions, including indications and contraindications for use, warnings, etc.

F Labeling/packaging

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

## 7. Efficacy Data

Product efficacy must be demonstrated by two independent adequately powered and well-designed randomized controlled clinical trials lasting at least six months. One multicenter clinical trial is also acceptable and may facilitate recruitment of a large study population needed for demonstration of a meaningful result. Depending upon the agent being studied and/or the claims being sought, some studies may require longer duration.

In the case of the sponsor seeking adjunctive claims, there would be three arms to the trial:

- (i) Positive control—which is scaling and root planing or predicate device or agent;
- (ii) Vehicle control plus scaling and root planing;
- (iii) Test agent plus scaling and root planing.

Scaling and root planing, as performed in the trial, must be defined (e.g., time of scaling each tooth). In order to determine the clinical value of a product, comparison should be made to scaling and root planing. At the present time, it is most likely that a new product to treat periodontitis will be used in the United States as an adjunct to scaling and root planing and this should be consistent in the design of studies for these products.

In the case that the sponsor is seeking approval of the test agent as a stand-alone treatment for periodontitis, there should be three arms to the trial:

- (i) Positive control – which is scaling and root planing or predicate device or agent;
- (ii) Vehicle control (vehicle is the inactive carrier used to deliver the test agent);
- (iii) Test agent alone delivered in the vehicle carrier

Clinical trials must be conducted on a US population. Outcome assessments must include the ability of the agent to slow, arrest or reverse the progress of periodontitis. A masked study is mandatory and split-mouth designs are not acceptable.

For anti-infective agents that target specific periodontal pathogens, analysis of the subgingival microbiota must demonstrate quantitative reductions in these targeted pathogens and these reductions must show statistically significant associations with changes in the clinical measures of periodontal status.

For host modulation agents, analysis of gingival crevicular fluid must demonstrate quantitative reductions in mediators of inflammation and/or key regulatory mechanisms involved with periodontal pathogenesis, and these reductions must show statistically significant associations with changes in the clinical measures of periodontal status.

## 8. Safety Data

Regardless of the route of administration or the specific active ingredient, the anti-infective or host modulation agent must be able to demonstrate its ability to achieve a desired clinical outcome within a known and acceptable

safety profile. Clinical studies must include examinations of oral soft tissue and teeth, toxicological studies, and microbiological profiles that should demonstrate that pathogenic, resistant or opportunistic micro-organisms do not develop over the course of the study. Host modulation agents should demonstrate that no adverse reactions occur.

**A Effect on oral soft tissues**

Evidence of the effects of anti-infective and host modulation agents on oral soft tissues should be provided.

Observations of soft tissues should be conducted in patients during the study for the development of abnormal conditions, such as candidiasis, oral ulcerations, or other manifestations of opportunistic organisms that proliferate and may lead to secondary mucosal conditions.

**B Effect on oral hard tissues**

Evidence of the effects of anti-infective and host modulation agents on oral hard tissues should be provided.

**C Toxicology**

Information submitted for products containing active chemotherapeutic agents shall include assessments of possible side effects of the active agent or adverse effects of the product formulation. These should include standard toxicological profiles depending on the particular agent. All products must submit data on the mutagenicity and the carcinogenicity of the product or its active agents. Data should also be provided on any other unique characteristics of the active formulation.

**D Microbiology**

Evidence of the effects on oral flora should be provided, including whether opportunistic, resistant or pathogenic organisms develop.

**9. Comprehensive Bibliography**

**10. Copies of all Relevant Studies, Including Proprietary Studies on the Product**

**11. Appendices**

Detailed description of test evaluation methods and any other defined areas.

### III. STATEMENTS TO BE USED FOR PRODUCTS CLASSIFIED UNDER THESE GUIDELINES, INCLUDING QUALIFIERS:

There will be a statement to be used with the product:

“The ADA Council on Scientific Affairs Acceptance of [Product name] is based on its finding that the product is effective in helping [slow/arrest/reverse] periodontitis when used as directed.”

### IV. REFERENCES FOR FURTHER EXPLANATION

1. Hyman FN, Welch ME, Cheever JR. Regulatory issues for evaluation of therapies to prevent or arrest disease progression. *Annals Periodontol* 1997; 2: 166-179.
2. Imrey PB, Chilton NW, Pihlstrom BL, et al. Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis. *J. Periodontol Res* 1994; 29:348–360.
3. Newman MG. Design and implementation of clinical trials of antimicrobial drugs and devices used in periodontal disease treatment. *Annals Periodontol* 1997; 2: 180-198.
4. Offenbacher S, Salvi GE, Beck JD, Williams RC. The design and implementation of trials of host modulation agents. *Annals Periodontol* 1997; 2: 199-212.
5. Page RC, Armitage GC, DeRouen TA, Genco RJ, Hujoel P, Jeffcoat MK, Kornman KS, William RC. Design and Conduct of Clinical Trials of Products Designed for the Prevention, Diagnosis and Therapy of Periodontitis: The American Academy of Periodontology, 1995; 1–54.
6. Paquette DW, Fiorellini JP. Clinical trials and the evaluation of new periodontitis therapies. *Current Opinion in Periodontology* 1994; 87–98.
7. Pihlstrom BL. Overview of periodontal clinical trials utilizing anti-infective or host modulating agents. *Annals Periodontol* 1997; 2: 153-165.
8. ADA Council on Scientific Affairs. Acceptance Program Guidelines for Clinical Trial Protocols. Chicago: American Dental Association, 2007.

## CLINICAL PROTOCOL GUIDELINES FOR CHEMOTHERAPEUTIC AGENTS TO SLOW, ARREST OR REVERSE PERIODONTITIS

The following guidelines are given for the design and conduct of clinical studies for the evaluation of agents to slow, arrest or reverse periodontitis. Additional information regarding clinical trials and clinical trial reporting can be obtained from the Council's *Guidelines for Clinical Trial Protocols* (see IVI References for Further Explanation). The benefit of periodontal therapy is best demonstrated by stabilization of clinical parameters of periodontal health. For products that accomplish their effectiveness by anti-infective or host modulation means, it is necessary to demonstrate significant reductions in clinical indices of periodontitis and include supporting data for the mechanism of action. In each study, the active product should be compared with a positive control (scaling and root planing), and a placebo non-active product plus scaling and root planing. Stand-alone therapies should show at least equivalent stability of periodontal health as thorough scaling and root planing. There should be ongoing evaluation of periodontal stability in non-treatment arms. Sites which exhibit attachment level loss of  $\geq 2$  mm occurring during the trials should be exited and treated by conventional methods, if appropriate. The 2 mm threshold may not be appropriate for all trials and may also depend on the measurement device used. The nature of the baseline disease diagnosis and the rate of expected change should be considered. In some cases the threshold may be more or less than 2 mm.

**Sample Size:** A sufficient number of subjects should be enrolled in the study to ensure that appropriate statistical tests can be performed to demonstrate efficacy and safety and to allow for dropout in long-term trials. Justification of sample size which provides adequate power ( $1-\beta$ ) and alpha level must be provided.

**Study Duration:** Studies of the efficacy of anti-infective and host modulation agents in periodontitis will be conducted for a minimum of six months; however, longer periods may be needed to show stability of effects. Full-mouth assessments will be taken at least at baseline (prior to the study) and at three month intervals.

**Study Design:** Studies submitted should present a clinical picture consistent with adult periodontitis. All subjects should be adults in general good health who exhibit periodontal sites with simultaneous evidence of clinical attachment loss, periodontal inflammation, and probing depth of at least 5 mm. Subjects with several such sites may allow more efficient research, particularly if sites are distributed throughout the dentition. Care should be taken to exclude subjects with Early Onset Periodontitis. Additional protocol-specified criteria for inclusion and exclusion of potential subjects should be defined as required for participant safety, study validity and study efficiency. These will depend on other particulars of each study. Except for those using highly reliable methods of birth control, women of child-bearing potential should be excluded from studies involving new medication categories unless adequate animal data are present to exclude teratogenicity. Products intended for treatment of all teeth should be tested using representative teeth, including both single- and multi-rooted teeth. Sites selected for treatment or use as controls should be deep enough to clearly indicate periodontitis (probing depth  $\geq 5$  mm), but not so deep as to make the loss of the affected tooth likely during the experimental period. Sites at teeth with radiographic evidence of periapical lesions should be excluded. Baseline variables including but not restricted to severity of existing disease, smoking, and subgingival microbiota may be used for site selection, stratification prior to randomization, or post-stratification for analysis. (However, use of such baseline variables as inclusion criteria limits generality of results, and analyses based on post-stratification must be interpreted with caution.) Because of fluid exchange among contiguous locations in a pocket or around the circumference of a tooth, only one treatment method per tooth should be used and proximate surfaces of adjacent teeth should not be assigned to different treatment arms. Multiple sites on the same tooth, or adjoining surfaces on different teeth, might be treated by the same therapy provided that data analysis accounts for potential dependence among responses at such sites.

The frequency of use of the product should be representative of the actual use of the product in practice. If patient application is part of therapy, the subjects should be instructed in the proper use of the product, but not necessarily supervised. Subjects

should not be taking concomitant medication that alters gingival appearance and/or bleeding or interferes with, or potentiates, the actions of study agents. Any other concomitant agents must be reported. Exclusion of other subjects, for example those with a history of smoking or those with aggressive types of disease from a study of chronic periodontitis, may omit useful information and an attempt should be made to stratify these subjects into the study design. Randomized parallel-arm designs are the most appropriate.

Due to the possible residual effect of some agents, use of a crossover design requires submission of evidence to show that sufficient time has been allowed for the first treatment washout to occur. For the most part, crossover designs are inappropriate for equivalency studies because the bias usually underestimates treatment differences sensitive to type II errors. Additionally, crossover designs may be inappropriate in the long-term studies required for adequate evaluation of effectiveness. Where possible there should be appropriate masking of study and control medications (e.g., color, taste, form).

Examiners should be masked to the therapy being tested in each subject and evidence of measurement of inter- and intra-examiner variance must be provided. Examiners should be calibrated at the beginning of the study and recalibrated if the study extends beyond six months or if the methodologies dictate. The conditions of scaling and root planing must be defined. Compliance of the subjects in the study must be monitored. In addition, a plaque and/or gingival index should be used to measure oral hygiene in each arm. Manufacturers are encouraged to submit their protocols for review before the start of the study.

#### **Efficacy Assessments**

Since the fundamental measurement of the outcome of periodontitis is tooth loss it is important to choose acceptable surrogates for that result. Efficacy of an agent can occur with the reduction of one or more of the surrogate variables (e.g., reduction in target organisms and/or binding, neutralizing or eliminating toxic products), but may have no apparent clinical effect. An anti-infective or host modulation agent must demonstrate a statistically significant and clinically relevant improvement or stabilization in measures of periodontal status.

Factors affecting clinical relevance to evaluate therapeutic benefits may include: a) the magnitude of the effects observed at targeted sites, b) the proportion of sites affected within individuals and c) the proportion of patients displaying therapeutic benefits.

In the absence of biologic rationale for any absolute criterion of clinical significance (such as “x” mm of clinical attachment level gain), such a minimally clinically significant effect is best expressed as a fraction of the effect of SRP. Acceptance would be based on the new product satisfying criteria of statistical significance as compared to the vehicle control and clinical significance with reference to the SRP-based positive control. Separate clinical significance criteria might be desirable for products intended for field and professional use.

#### **Primary Outcome Variables**

All clinical trials must include clinical attachment level a primary outcome variable. Bone level changes may also be included as a primary outcome variable.

##### **A Attachment levels**

Measurement of clinical attachment levels is a standard for documenting changes in periodontal support. Attachment levels may be determined by using conventional hand-held probes marked in increments suitable for the purposes of the study or automated pressure-controlled probes. Attachment levels can be relative, using stents or disc-type devices, or clinical using fixed points on a tooth (e.g., cemento-enamel junction).

**B Alveolar bone changes**

Radiographic measurements of the alveolar bone changes using standardized methods can indicate both beneficial and pathologic changes in alveolar bone support. While the metabolic and temporal relationships to attachment level changes have yet to be resolved the use of imaging techniques such as computer assisted digital radiography may be considered as primary outcome measurements. Examples may include measurements of changes in alveolar bone height, density and/or volume.

**Secondary Outcome Variables**

Secondary variables may be used to support the primary outcome variables.

**C Probing depth**

Probing depth measurements may be determined by using standardized conventional hand-held probes marked in increments suitable for the purposes of the study or automated pressure-sensitive probes.

**D Bleeding on provocation**

Bleeding should be assessed using a recognized index and evaluating for the presence or absence of bleeding following probing.

**E Microbial assessments**

Microbial assessments to support efficacy claims for anti-infective agents and for agents with antimicrobial effects shall be performed by demonstrating reduction of periodontal pathogens. For studies of anti-infective agents microbial samples should be incorporated into the design of the study and taken at least at baseline and at the end of the study. These samples may be taken from patient sub-sets.

**F Biochemical, metabolic by-products**

Quantitative measurements of host response mediators may be evaluated. Inflammatory mediators and markers of tissue destruction may be used as measures of sub-clinical inflammation. These samples may be taken from patient sub-sets.

**Statistical Analysis**

Measurements should be obtained and reported for the observational unit most biologically appropriate for treatment evaluation, whether this be the site, tooth, quadrant, whole mouth, or other unit. The choice of unit should be justified in documentation, and inferences regarding therapeutic performance should be directed at this unit. Methods of formal statistical inference may be parametric or non-parametric, as most appropriate. Analyses should adjust for possible intra-subject correlations between outcomes obtained from different observational units. (When designing a trial, it is in the researchers' interest to account for the impact of such intra-subject correlations on statistical power.)

Currently, the mean change from baseline among sites receiving similar therapeutic intervention is a preferred summary statistic for representing the behavior of clinical attachment level, bone support, or probing depth subsequent to therapy. Therapeutic activity may be assessed by comparing mean change after use of the product with mean change after treatment with control therapy. Within the context of this basic approach, it may be appropriate to stratify sites by baseline clinical attachment level or probing depth, and/or other variables.

Descriptions of important variables, whether clinical factors or outcomes, should provide information about distribution shape as well as summary statistics. Major outliers should be noted, their clinical feature documented, and impact on conclusions assessed.

Data on teeth and patients taken off protocol should be reported in detail. Reporting numbers of off-protocol teeth by treatment provides some reassurance against gross biases due to dropped teeth, but is insufficient by itself. All data for off-protocol teeth should be maintained in the data base, and employed appropriately in analyses which duly consider the “intention to treat” principle.

Data on population compositions, therapeutic monitoring and compliance where relevant, and data quality control should be collected throughout the conduct of a trial. Summaries should be included in submission to the Council.

Quality control studies of reliability will generally involve repeated observations on a set of subjects. For continuous variables, reliability might be summarized by coefficients of variation and intra-class correlation coefficients. For categorical variables, percent agreement scores and associated kappa statistics might be used. Statistics supporting measurement reliability should be properly interpreted in the context of the measurement instrument. For example, probing depth may be measured using a conventional probe with mm., demarcations, and reported to the nearest mm. In that case, a low standard deviation from replicate probing depths documents high reproducibility, but does not show that probing depth can be measured more accurately than to the nearest millimeter. That can only be demonstrated by validation against a more accurate reference device, such as a probe with finer demarcations which can also be read reproducibly. Control of examiner variation through design is always desirable, and analytic adjustments are helpful, but these do not substitute for basic measurement quality control procedures throughout the conduct of the study.

Analysis of the safety data must be done with appropriate statistical techniques.

#### **Safety Assessments**

Safety assessments may be made at each measurement period. Additional safety assessments may be made to supplement safety profile data for products being tested.

1. Oral soft tissue assessments.
2. Assessment of teeth and restorations.
3. Microbiological assessments.

Evidence should be provided that the development of resistant microorganisms or emergence of periodontal pathogens does not occur with the use of the product. It should be demonstrated that microbes associated with periodontitis, opportunistic organisms such as yeasts and Gram-negative enteric bacteria, do not emerge sub- or supragingivally during the course of the study.

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