

Acceptance Program Requirements



Chemotherapeutic Products for Control of Gingivitis

Acceptance Program Requirements

This document outlines specific category requirements. Please also refer to the General Guidelines for Participation in the ADA Seal of Acceptance Program.

- Category:** Chemotherapeutic Products for Control of Gingivitis
- Purpose:** The Acceptance Program applies to over-the-counter dental products for which safety and efficacy has been established by laboratory and/or clinical evaluations where appropriate. Accordingly, the purpose of these requirements is to provide a structure upon which chemotherapeutic products for control of gingivitis can be considered for ADA Acceptance.
- Scope:** These requirements apply to products used for the control of gingivitis and, if applicable, supragingival dental plaque, through the use of chemotherapeutic agents. Products that control gingivitis solely by the mechanical removal of plaque will not be considered by these Requirements. Examples of products evaluated under these Requirements include mouthrinses and dentifrices containing agents that would destroy, inhibit, or modify plaque, including its pathogenicity for gingivitis, and microbiologic growth in general, products that modify the attachment of plaque microorganisms to their natural sites, and products that act by other antimicrobial mechanism to reduce or prevent gingivitis.

Notice Regarding Submission of Copyrighted Materials: To make the review of submissions to the ADA Acceptance Program as efficient as possible, the Council on Scientific Affairs provides copies of submitted materials to Council members and consultant reviewers, and also posts submitted materials to an area of the ADA's web site the access to which is restricted to Council members and staff.

By making a submission, you are representing and warranting to the Council on Scientific Affairs and the ADA that you have obtained sufficient permission(s) from the copyright owner(s) of any copyrighted material included with your submission to allow for the publication and distribution of that material by the ADA as described above, and agree to indemnify and hold ADA harmless from any and all claims arising from such publication or distribution.

Questions can be directed to adaseal@ada.org.

1. **SEAL STATEMENT**

The following statement applies to products approved under the below-listed criteria:

“The ADA Council on Scientific Affairs’ Acceptance of (Product Name) is based on its finding that the product is safe and has shown efficacy in helping to prevent and reduce gingivitis (and plaque above the gumline), when used as directed.”

Format for product packaging:

- Helps prevent and reduce plaque
- Helps prevent and reduce gingivitis (when whole mouth gingivitis is measured)
- Helps prevent and reduce gingivitis between teeth (when interproximal gingivitis is measured)

2. **SUBMISSION DIRECTIONS**

- A. Submissions are to be sent in electronic format (email) to adaseal@ada.org. Additional instructions will be provided regarding shipment of necessary samples.
- B. The submission fee is a one-time, non-refundable fee and is required before review begins. Maintenance fees are billed to the company in January of every year.
- C. The review timeline for new submissions is typically 4-6 weeks after all materials have been received. The decision to award the ADA Seal to a new product is made by the Council on Scientific Affairs. Family submissions may take anywhere from 2-4 weeks to review. Eligibility criteria for Family Submissions are outlined in the Guidelines for Participation in the ADA Seal of Acceptance Program.

Note: This is an estimated timeline. Extended review time may be required if additional information or clarification is needed from the manufacturer.

- D. When a product is classified as “Accepted” and is awarded the ADA Seal of Acceptance, the Acceptance period is five years. Manufacturers will be contacted approximately six months before the expiration of the current Acceptance period to complete the requirements for the next five-year Acceptance period.
- E. Classification of a product under the Acceptance Program is subject to the conditions stated in the Agreement Governing Use of ADA Seal of Acceptance.
- F. Guidelines for the design and conduct of clinical studies are provided in Appendix I. Manufacturers interested in seeking the ADA Seal of Acceptance are encouraged to submit their clinical protocols to the Council for review prior to the start of clinical studies.

3. SUBMISSION MATERIALS

All submissions must include the following information based on product type and comply with the 'General Criteria for Acceptance' described in the Guidelines for Participation in the ADA Seal of Acceptance Program.

A. Product Information

- i. Name of product(s)
- ii. Name of company
- iii. FDA Documentation
 - a) FDA registration and product listing must be provided.
 - b) Evidence of FDA approval to market, if applicable (e.g., 510 (k) letter, pre-market approval, NDA/Evidence of FDA registration).
- iv. Product Claims
 - a) Products approved under these category requirements may receive the following Seal bullet claims: helps prevent and reduce plaque; helps prevent and reduce gingivitis; helps prevent and reduce gingivitis between teeth. Data required to substantiate efficacy towards the Seal bullet claim is explained in Section C below. ***Please provide a list of all additional safety and efficacy claims beyond the Seal bullet claim. These claims should follow the ADA Brand Standards and must undergo review and approval by the Council on Scientific Affairs before they can be included on product packaging.*** Substantiation for any health benefit claims, outside of the Seal bullet claims, must be provided through clinical and/or laboratory data specific to the product and is not addressed in Section C below. Whether clinical or laboratory data is required depends on the nature of the claim. For any questions regarding claim substantiation, please contact the ADA Seal Program.
 - b) NOTE: Non-fluoride products submitted under this category alone cannot include a Seal bullet claim for cavity prevention. However, if the product includes a cavity prevention claim beyond the Seal bullet claim anywhere on the packaging, evidence of efficacy and safety in the reduction of dental caries must be provided. At least one clinical trial will be required. Please refer to the Clinical Protocol Guidelines for Caries in the ADA Seal Fluoride Dentifrice Category Requirements.
- v. Product Specifications
 - a) Chemical composition or components of the product and purpose of the various ingredients. To facilitate review, submitting the chemical composition, concentration, and purpose in tabular form is recommended.
 - b) Material Safety Data Sheet (MSDS) (if applicable).
 - c) Design of the product (if applicable).

- vi. Product Manufacturing**
 - a) Describe or list the quality procedures for manufacturing or testing of the product which demonstrate compliance with Good Manufacturing Practices.
 - b) Certification of Good Manufacturing Practices can also be provided.
- vii. Product Instructions**
 - a) Include detailed instructions for product use.
 - b) Include indications and contraindications for use, warnings, etc.
- viii. Product Labeling/Packaging**
 - a) All labeling/packaging should follow the ADA Brand Standards and must be approved by the Council on Scientific Affairs before use. Companies may submit draft copy for approval. See iv. Product Claims above.
- ix. Product Samples**
 - a) Submission requires three samples, one from three different production lots for analysis by the ADA Laboratories.

B. Safety Data

- i. Data supporting product safety should include clinical studies in which oral soft tissues and teeth are examined and appropriate toxicological and microbiological studies demonstrating that pathogenic or opportunistic microorganisms are not selected for over the course of the study. See Appendix I for details. Compliance with applicable FDA standards should be provided, where appropriate.
- ii. All submitted oral rinses must meet ANSI/ADA Standard No. 116 or ISO 16408, Dentistry – Oral Care Products – Oral rinses. Tests include pH, heavy metals, compatibility with oral tissues, microbial contamination, stability, and readily fermentable carbohydrates.
- iii. All submitted dentifrices must meet ANSI/ADA Standard No. 130 or ISO 11609, Dentistry - Dentifrices - Requirements, Test Methods and Marking. Tests include pH, heavy metals, compatibility with oral tissues, microbial contamination, stability, and readily fermentable carbohydrates.

C. Efficacy Data

- i. Product efficacy must be demonstrated by two independent and registered clinical studies of at least three months utilizing a placebo control. Studies should assess the ability of a chemotherapeutic agent to prevent or reduce gingivitis and to inhibit or reduce plaque formation or plaque pathogenicity.

ii. **Surrogate Studies:** In some cases where a submitted product contains the same active agent(s) that is/are contained in products that have received the ADA Seal based on the results of clinical safety and efficacy studies from the same manufacturer, surrogate testing will suffice in lieu of clinical studies. The Council makes the determination when surrogate testing is appropriate. Surrogate tests for mouthrinses are described in Appendix II.

D. **Supporting Literature:** Copies of the most significant articles or supporting literature demonstrating safety or efficacy of the product should be provided, where applicable.

4. **REFERENCES**

The following references were used in the development of these requirements and can be consulted for a more detailed discussion:

- ANSI/ADA Standard No. 116 – Oral Rinses 2020
- ISO 16408:2015, Dentistry – Oral Care Products – Oral rinses
- ANSI/ADA Standard No. 130 Dentifrices – Requirements, Test Methods and Marking 2020
- ISO 11609:2017, Dentistry - Dentifrices - Requirements, Test Methods and Marking
- ADA Brand Standards: https://www.ada.org/-/media/project/ada-organization/ada/ada-org/files/resources/research/seal/ada_seal_brand_standards_nov2024.pdf

Appendix I Clinical Protocol Guidelines for Chemotherapeutic Products for Control of Gingivitis

The following guidelines are given for the design and conduct of clinical studies for the evaluation of chemotherapeutic agents to provide evidence of efficacy and safety in the control of gingivitis and, if applicable, supragingival plaque. The clinical benefit of plaque control can best be demonstrated by a significant reduction in gingivitis. For products that accomplish their antigingivitis effectiveness through plaque reduction, it will be necessary to demonstrate statistically significant reductions in both plaque and gingivitis. For products that do not exert their antigingivitis effect through plaque reduction, it will be necessary to demonstrate a statistically significant reduction in gingivitis and supporting data for the mechanism of action. Manufacturers are encouraged to submit their clinical protocols to the Council for review prior to the start of clinical studies.

Study design: Clinical trials should be randomized whenever possible, with participants allocated to treatments through a randomization process. Designs employing either crossover or parallel groups are acceptable. Because of a possible retained effect of some agents, care must be taken in a crossover design to include an adequate latent period between study periods. Additionally, the crossover design may not be practical in the long-term studies required for adequate evaluation of product efficacy. Studies should be blind regarding participants, examiners and data analysts; when blinding is not possible, a justification must be provided. IRB approval is required for all studies involving human subjects. The frequency of use of the product should be representative of actual use of the product in practice; and the user should be instructed in the proper use of the product but not necessarily supervised. Studies must report all treatment groups, and an attempt should be made to assess the level of compliance of the subjects in the study. If a protocol is designed to test a product to be used for a specific indication, where a pre-prophylaxis baseline is not required, for example, a reduction in existing gingivitis claim, appropriate modifications should be made in the study. Studies should be conducted for at least 3 months, with measurements being taken at baseline, at three months, and at an (optional) intermediate period.

Number of studies: At least two studies should be conducted at a different site and including a separate participant pool. Studies are expected to be independent, and free from direct control from the manufacturers. Studies are expected to adhere to the CONSORT guideline, and the checklist should be completed and uploaded with the submission.

Sample size: The protocol should describe how sample size was determined, including all assumptions supporting the calculation and clearly defining the primary and secondary outcome variable(s) for which the study is being powered. A power of at least 80%, at an alpha error of 5%, is expected for variables leading to a Seal claim.

Eligibility criteria: Trial participants should be representative of the population for which the product is intended. Inclusion and exclusion criteria for participant's enrollment should be clearly described. Each subject will have a complete oral examination to determine eligibility for the study, with both genders and representative age groups included according to intended use. Subjects should not be taking medication which alters gingival appearance/bleeding. Furthermore, they should not have taken such medications within one month of initiation of the study. Other criteria for inclusion/exclusion of subjects must be provided.

Test product and comparator: The test product should be compared with standard of care products/methods as defined by the ADA. Clear determination is to be made about the goal of the study to show superiority, equivalence or non-inferiority.

Clinical procedures: The phases of the study (lead-in, test, wash-out, when applicable) should be clearly described, preferably using a diagram. The instructions given to participants regarding any study-specific procedures should be clearly described. The duration of the study, and when assessments will be performed, must be clearly described. For studies involving evaluators, their number and calibration methods should be provided, as well as intra/inter examiner agreement data. When the indices used allow accurate repeated

measures, it is necessary to provide a measure of intra- and inter-evaluator variance. Examiners should be capable, at a minimum, of replicating their own scores to a high degree on a site-by-site basis.

Assessments for efficacy: Variables assessing efficacy should be clearly described and allow for a comparison between the test product and the comparator. Only products that significantly reduce both plaque and gingivitis may claim plaque control. If a product demonstrates significant plaque reduction without a concomitant significant reduction in gingivitis, it is not eligible for Acceptance.

Gingivitis Assessments: Methods should be selected that measure gingivitis using both subjective and objective criteria. The comprehensive Löe & Silness gingival index which incorporates both bleeding and visual appearance can be used. Alternatively, the visually based Modified Gingival Index can be used along with an index of gingival bleeding, such as the Eastman Interdental Bleeding Index. Full mouth evaluations including 6 sites per tooth (mesio-buccal, disto-buccal and mesio-lingual, lingual, disto-lingual) on a minimum of 20 teeth should be performed for studies aimed at evaluating whole mouth gingivitis. For claims focused on interproximal gingivitis reduction, 4 interproximal sites per tooth (mesio-buccal, disto-buccal and mesio-lingual, disto-lingual) on a minimum of 20 teeth should be evaluated.

Plaque Assessments: Plaque will be scored before and after brushing at each examination using the Turesky modified Quigley-Hein Index, or another appropriate and validated index. Full mouth plaque evaluations should be performed.

Antimicrobial Susceptibility Testing should be performed in accordance with methods recommended by the Clinical and Laboratory Standards Institute (CLSI). This includes the use of commercial U.S. Food and Drug Administration-cleared manual or automated antimicrobial susceptibility testing systems. Bactericidal activity should be assessed using minimal bactericidal concentration (MBC) or kill time methods. Where appropriate, the number of colony forming units should be less than 0.1% of the initial inoculum count to demonstrate a 99.9% kill. A variety of aerobic and anaerobic microbial species (8-10) representing organisms associated with oral health and disease should be used. See Appendix II for examples. Alternative microbiological methods may also be acceptable. Manufacturers are encouraged to submit a description of such methodologies to the Council for review.

Assessments for safety: Variables assessing safety should be clearly described and allow for a comparison between the test product and the comparator. Evidence that the product does not adversely affect oral soft and hard tissues and restorations. should be provided. Subjects should be examined in the course of the three-month studies for the presence of pathologic conditions such as oral ulceration, candidiasis, or other secondary infections of the oral mucosa that may be manifestations of the proliferation of opportunistic microorganisms.

Toxicology: Information submitted for products containing chemotherapeutic agents shall include assessments of possible toxic effects of the active agent or adverse effects of the product formulation. These should include standard toxicological profiles depending on the particular product. All products must submit data on the mutagenicity and the carcinogenicity of the product or its active agents. It is also recommended that data be provided on the effect of the product, if any, on taste sensation, staining of oral tissue, or other characteristics that may be unique to the formulation.

Microbiological Assessment: The objective of the microbial safety assessment of plaque is to determine whether there are shifts in the balance of pathogenic or opportunistic flora that might have an adverse effect on oral tissues or contribute to the progression of microorganisms in the flora from non-periodontal pathogens to those that are pathogenic. Plaque should be harvested in such a way from the areas chosen for sampling that an objective evaluation of the flora can be made. It is suggested that the sample be recorded as recoverable counts per representative pooled plaque sample from the individual. Methods that require that total plaque be harvested from each area chosen for sampling and counts recorded as either counts per tooth or counts per milligram of wet plaque weights are acceptable as an additional method of documentation. Microbiological plaque samplings should be incorporated into the design of the study and taken at the beginning and end of the study for control and test groups. It is recommended, but not required, that

consideration be given to include a microbiological assessment of post-treatment plaque in the study design. A subset of the participants would be acceptable for samplings at selected time periods.

- i. **Estimates of total plaque bacteria**
Plaque samples of a subset representative of the population in the study should be collected and grown in a nonselective medium. A count of bacteria should be made to estimate total bacterial load.
- ii. **Estimates of representative plaque bacteria**
Plaque samples should be grown on media selective for appropriate representative groups of microorganisms. The use of dark-field or phase contrast microscopy would be an additional method suitable for identifying motile forms. A count and microscopic analysis should be made to estimate plaque content of representative populations of microorganisms that are normally found in plaque or are associated with gingivitis.
- iii. **Shifts in pathogenic or opportunistic organisms**
The data should clearly characterize the oral flora in the control group compared with the test group in terms of normal populations identified in supragingival plaque. The three-month study should demonstrate that although a shift or change in the species of these bacteria may occur, a shift to predominately gram-negative, anaerobic, and motile forms should not occur. It shall be demonstrated that microorganisms that have been associated with periodontitis do not develop supragingivally during the course of a clinical study. Opportunistic organisms (such as yeasts and gram-negative enteric bacteria) shall also not develop during the study.

Statistical analysis: Depending on the type of study (superiority, equivalence, non-inferiority), the statistical analysis plan should be described allowing for a comparison between the test product and the comparator, for all study variables, considering the predetermined power and significance level. Mean group whole mouth scores for plaque and gingivitis on all surfaces will be compared at baseline, three months, and at an (optional) intermediate period with appropriate statistical tests. If more than two groups are being evaluated appropriate multiple comparison tests should be used. The basis for statistical sizing must be provided in the protocol. Information to be provided includes expected examiner variance, the targeted alpha and beta values, the estimated drop-out rate, and the targeted treatment differences.

A pooled average of at least 10% (using the Modified Gingival Index) or 15% (using the Löe and Silness Gingival Index) compared to the placebo control are required to demonstrate a reduction in gingivitis; the confidence interval must be provided. Plaque measurements shall demonstrate that quantitative plaque reductions or reductions in plaque pathogenicity are statistically significantly different from the placebo control.

Where appropriate, a non-parametric test will be used to assess safety evaluation data (normal vs. abnormal).

Appendix II Surrogate Tests for Anti-Gingivitis Mouthrinses

Chemical Equivalence:

1. Ingredient breakdown
2. Analysis with gas chromatography

Assessments for safety:

Irritation/Sensitization Test

(Note: Subjects with known allergies should not participate.)

Administration of test products:

A. Phase I (Challenge Period for Irritation)

Subjects should rinse with 20 mL of the test mouthrinse for 30 sec, under supervision at each of 5 hourly intervals, on five consecutive days.

During the study, subjects should follow their usual dietary and oral hygiene procedures but should refrain from using any breath freshener product in order to reduce alternate sources of potential irritation. Following the five-day irritation/induction period, subjects should go off treatment for 18 days.

B. Phase II (Challenge Period for Sensitization)

After an 18-day rest period, subjects should rinse with 20 mL of the test mouthrinse for 30 sec under supervision at 5 hourly intervals for one day.

Examination procedure:

A. Examiner

All oral examinations should be conducted by a dentist with experience in human clinical evaluation of oral products. The examiner should not have access to previous findings prior to any examination.

B. Clinical Criteria and Examination Schedule

The oral mucosae should be examined prior to the initiation of treatments to determine freedom from gross inflammation, irritation or other pathology. Phase I and Phase II results should be recorded.

- Phase I: Subjects should be examined for evidence of irritation or inflammation on days 1, 3, and 5, one hour after the final daily rinsing with the test mouthrinse.
- Phase II: Subjects should also be examined prior to the first challenge treatment, then again 1 hour and 24 hours after the fifth challenge application.

C. Clinical Criteria

The examiner should rate the condition of the intraoral soft tissues as normal or abnormal and describe the condition using the following scale and description:

0	no reaction (normal)
±	barely visible (any discernible change in the color, i.e., erythema)
1	erythema plus slight edema
2	moderate erythema and/or edema (beginning of tissue breakdown or slough)
3	severe inflammation/irritation (definite blistering ulceration or epithelial slough)

Assessments for efficacy:

Demonstrate that the product is equivalent to a clinically tested, Accepted product from the same manufacturer in terms of antimicrobial activity. Antimicrobial susceptibility testing should be performed in accordance with methods recommended by the Clinical and Laboratory Standards Institute (CLSI). This includes the use of commercial U.S. Food and Drug Administration-cleared manual or automated antimicrobial susceptibility testing systems.

Bactericidal activity should be assessed using minimal bactericidal concentration (MBC) or kill time methods. Where appropriate, the number of colony forming units should be less than 0.1% of the initial inoculum count to demonstrate a 99.9% kill.

A variety of aerobic and anaerobic microbial species (8-10) representing organisms associated with oral health oral health and disease should be used. Examples include:

- *Actinomyces naeslundii*
- *Actinomyces viscosus*
- *Aggregatibacter actinomycetemcomitans*
- *Bacteroides loeschii*
- *Campylobacter rectus*
- *Eikenella corrodens*
- *Fusobacterium nucleatum*
- *Porphyromonas gingivalis*
- *Prevotella intermedia*
- *Tannerella forsythia*
- *Treponema denticola*
- *Wolinella recta*

Other Organisms Associated with Oral Health and Disease

- *Lactobacillus casei*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*

Alternative microbiological methods may also be acceptable surrogate tests. Manufacturers are encouraged to submit a description of such methodologies to the Council for review.

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