

Acceptance Program Requirements



Fluoride-Containing Dentifrices

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:	Fluoride-Containing Dentifrices
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 fluoride-containing dentifrices can be considered for ADA Acceptance.
Scope:	These requirements apply to fluoride-containing dentifrice products used for the control of dental caries. Such products may further contain active agents to control other dental indications such as hypersensitivity, gingivitis, and plaque. However, these requirements only address the requirements necessary to determine the anti-caries efficacy of such products. Each additional clinical indication will require further evidence of safety and efficacy as defined in the appropriate requirements.
Notice Regarding Submission of Copyrighted Materials:	<p>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.</p> <p>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.</p>

Questions can be directed to adaseal@ada.org.



1. SEAL STATEMENT

The following statement applies to fluoride containing dentifrices 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 prevent tooth decay when used as directed.”

Format for product packaging:

- Helps prevent cavities

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 will receive the following Seal bullet claim: helps prevent cavities. 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.
- 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. Evidence must be provided that the components of the product are safe for use in the oral cavity. When appropriate, standard toxicological, mutagenic, and/or carcinogenic testing may be required. Compliance with applicable FDA standards should be provided (where appropriate).
- ii. In cases where new agents that do not appear on the Generally Recognized as Safe (GRAS) list have been introduced into a fluoride dentifrice, clinical studies must be submitted which include examinations of oral soft and hard tissues, toxicological studies, and microbiological profiles that should demonstrate that pathogenic or opportunistic microorganisms do not develop over the course of the study (Appendix II). Also, there may be occasions where an ingredient has an established record of safe use in the oral cavity but does not appear on the GRAS list. In this case, the clinical testing specified in these requirements may not be necessary, but the manufacturer should supply supporting data and a rationale for it being considered safe to use in the dentifrice.
- iii. All submitted dentifrices must meet ANSI/ADA Standard No. 130 or ISO 11609, Dentistry - Dentifrices - Requirements, Test Methods and Marking. Test reports must include total fluoride, heavy metals, pH, microbiology, abrasivity, stability, and readily fermentable carbohydrates.



C. Efficacy Data

- i. In addition to the standard laboratory tests specified for safety, manufacturers are required to submit laboratory tests which may be predictive of clinical use/behavior of dentifrice formulations that adhere to the FDA Code of Federal Regulations and contain GRAS ingredients. These tests are presented in Appendix I and include:
 - a) Available fluoride in fresh and aged samples
 - b) One minute fluoride release in fresh and aged samples
 - c) Bioavailability in demineralized enamel
- ii. For new dentifrice formulations, or those that include a new fluoride species, a new abrasive compound, or a fluoride concentration not approved for marketing in the FDA OTC Monograph on Anticaries Drug Products for OTC Human Use, caries clinical trials will be required. The clinical design requirements for caries studies are presented in Appendix II.
- iii. For products that also contain active agents for other purposes (e.g. stain removal), relevant and additional ADA Acceptance Program Requirements must also be satisfied, as appropriate.

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. 130 Dentifrices – Requirements, Test Methods and Marking 2020.
- ISO 11609:2017, Dentistry - Dentifrices - Requirements, Test Methods and Marking.
- Food and Drug Administration Code of Federal Regulations Title 21, Volume 5; 21CFR355.50 Labeling of anticaries drug products.
- 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 Experimental Design Protocol for Dentifrices

This category relates to required laboratory data for dentifrice formulations that do not contain a new fluoride source or abrasive compound. The design of each profile study must either be in accordance with existing recognized research methodology or must be justified by the manufacturer.

1. Available Fluoride in Fresh and Aged Samples

- A. Data: Chemical data must be submitted to document that the active fluoride agent is chemically free and available in both fresh and aged samples. At least 90% of the labeled amount of fluoride must be available in both fresh and aged samples. Fresh samples are defined as those prepared and analyzed within one month of formulation. Aged samples are defined as product compositions at the effective end of their expiration period. These samples can be aged either under normal, representative conditions, or by high temperature accelerated aging. In addition, the manufacturer must submit laboratory data to demonstrate the effect of both dilution and pH on the product as compared with clinically tested formulations of compositional equivalence.
- B. Methods: Available fluoride measurements can be performed using ion-selective electrode or ion chromatography. See ANSI/ADA Standard No. 116 Oral Rinses or ISO 16408 Dentistry – Oral hygiene products – Oral rinses for an example ion-selective electrode method. It is suggested that samples be prepared by diluting 1.00 ± 0.10 gram (accurate to 0.01 gram) in about 15 mL of deionized water, completely homogenizing, diluting to 100 milliliters with deionized water, mixing thoroughly, centrifuging, and filtering the supernatant. Samples should be prepared in duplicate and available fluoride measurements should be averaged. Appropriate standard solutions should be prepared. (Other validated methods will be considered).
- C. Equation:
- $$\text{Available Fluoride (ppm)} = \frac{\text{Fluoride Concentration of Sample Solution (ppm)} \times 100}{\text{Weight of Dentifrice (g)}}$$

2. One Minute Fluoride Release Rate in Fresh and Aged Samples

- A. Data: Chemical data must be submitted to show that at least 80% of the labeled amount of fluoride must be released by the test formulation in fresh and aged samples within one minute of homogenization within a 1:4 dilution with water or saliva (human or artificial).
- B. Method: One minute fluoride release rate measurements can be performed using ion-selective electrode or ion chromatography. See ANSI/ADA Standard No. 116 Oral Rinses or ISO 16408 Dentistry – Oral hygiene products – Oral rinses for an example ion-selective electrode method. It is suggested that 4.00 ± 0.10 grams (accurate to 0.01 gram) of sample be diluted with deionized water equal to exactly 3 times the sample weight and homogenized for exactly 60 seconds followed by immediate centrifugation and immediate supernatant filtration. Samples should be prepared in duplicate and one minute fluoride release rate measurements should be averaged. Appropriate standard solutions should be prepared. The dilution factor for the one-minute release rate can be determined by ion chromatography. It is suggested that 4.00 ± 0.10 grams (accurate to 0.01 gram) of sample be diluted with a stock standard of 100 ppm bromide or nitrite equal to exactly 3 times the sample weight, completely homogenized, centrifuged, and supernatant filtered before measuring the concentration of bromide or nitrite. Samples should be prepared in duplicate and bromide/nitrite measurements should be averaged. Appropriate standard solutions should be prepared. (Other validated methods will be considered).
- C. Equations:
- $$\text{Released Fluoride (ppm)} = [F] \times \text{Dilution Factor},$$
- where [F] = Fluoride Concentration of Filtrate of Sample Solution (ppm)

$$V1 \times C1 = V2 \times C2$$
$$\text{Dilution Factor} = \frac{V2 - V1}{\text{Wt. of Dentifrice (g)}} + 3,$$

where V1 = Weight of working standard (g) = Volume of working standard (mL)

C1 = Concentration of working standard of Br⁻ or NO₂⁻ (ppm)

V2 = Volume of total liquid in the slurry

C2 = Concentration of Br⁻ or NO₂⁻ (ppm) in the supernatant

3. Bioavailability in Demineralized Enamel

- A. Method: Each test dentifrice must demonstrate an ability to deliver and incorporate levels of fluoride into demineralized enamel equivalent to clinically tested formulation(s). In general, demineralized enamel refers to subsurface lesions produced in enamel that are a result of a short-term acidic treatment within a solution partially saturated with respect to hydroxyapatite. The specific methodology to be used in preparing the needed demineralized lesion is optional. However, the rationale for utilizing a particular technique must be justified. Minimally, each study must contain: an appropriate placebo (test product minus active fluoride agent), test product in a formulation equivalent to that to be manufactured, and the clinically tested formulation or ADA Accepted compositional equivalent containing the same active agent/abrasive system.
- B. Statistical evaluation: The statistical analysis of each study must clearly separate the test product from the placebo and strongly suggest that the test formulation is equivalent to a clinically tested formulation(s). These studies must have adequate statistical power. Manufacturers are responsible for the statistical analysis of their results.

Appendix II Caries Clinical Design Protocol for Fluoride Dentifrices

The following guidelines are provided for the design and conduct of clinical studies to generate evidence for the evaluation of safety and efficacy of new fluoride-containing dentifrices that contain new fluoride compounds, new abrasive systems, combinations of fluoride compounds, or fluoride concentrations not contained in the FDA Monograph for Anti-Caries Products for OTC Human Use. These guidelines attempt to define minimal requirements necessary to provide evidence of efficacy and safety in the reduction of dental caries. Manufacturers are encouraged to submit their clinical protocols to the Council for review prior to the start of clinical studies. The information indicated below is applicable to each independent clinical study.

Number of studies: At least two studies should be conducted at a different site and including a separate participant pool. One study may be waived by the Council when appropriate supporting clinical data exist. Studies are expected to be independent, and free from direct control from the manufacturers. At least one study should be performed in the target population, and another may be in a high-risk population. Studies are expected to adhere to the CONSORT guideline, and the checklist should be completed and uploaded with the submission.

Sample size: A sufficient number of subjects should be enrolled to ensure that appropriate statistical tests can be performed. 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. It is recommended that participants taking medications that may affect the oral microbiota during the course of the study should be excluded (unless this is the intended population of the study).

Test product and comparator: The test product should be compared with an established, clinically proven positive control. 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. The study should be conducted for a minimum of two years, preferably three. Measurements should be taken at least at baseline (prior to the study), at the conclusion of the study, and at an intermediate time period.

Assessments for efficacy: Variables assessing efficacy should be clearly described and allow for a comparison between the test product and the comparator. Caries lesions at the cavitated level must be used as the marker of disease. Incipient lesions may be monitored as secondary markers.

Assessments for safety: Variables assessing safety should be clearly described and allow for a comparison between the test product and the comparator. Evidence for potential effects of any new agents on oral soft tissues should be provided, including observation of abnormal conditions such as candidiasis, oral ulcerations, and other manifestations of opportunistic microorganisms. Evidence of effects on oral hard tissues and dental restorations should also be supplied. Information on possible toxic effects and adverse



reactions should be included, via standard toxicological profiles. Monitoring for changes in oral microbiota to detect opportunistic or pathogenic organisms should also be performed.

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 caries (e.g. DMFT or DMFS) should be compared at baseline, at an intermediate period, and at the termination of the study.

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