

Acceptance Program Requirements



Products for the Temporary Relief of Oral Discomfort



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:** Products for the Temporary Relief of Oral Discomfort
- 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 products used for temporary relief of oral discomfort can be considered for ADA Acceptance.
- Scope:** These requirements apply to topically applied products for the temporary relief of oral discomfort. Products evaluated using these requirements are thought to relieve discomfort and/or pain of the oral soft tissue through analgesic or other efficacious properties.
- 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 temporarily relieve discomfort of mouth sores, when used as directed.”

Format for product packaging:

- Helps temporarily relieve discomfort of mouth sores

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 temporarily relieve discomfort of mouth sores. 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. If the product contains ingredients not on the generally recognized as safe (GRAS) list, at least one six-month clinical safety study may be required. See Appendix for details regarding clinical protocol guidelines.
- iii. Safety must be demonstrated by the absence of irreversible side effects resulting from the use of the product. Documentation of adverse events during all phases of clinical testing are required.
- iv. For those products containing active ingredient(s) included in the FDA monograph on OTC Relief of Oral Discomfort, laboratory assays showing the concentration within $\pm 10\%$ of the labeled amount are required.
- v. Those products with active ingredients that are not covered by the FDA monograph on OTC Relief of Oral Discomfort must conduct clinical studies demonstrating product safety. See Appendix for details regarding clinical protocol guidelines.
- vi. Products that contain benzocaine must mention a warning about methemoglobinemia and directions for safe use. Suggested wording is as follows:
 - **"METHEMOGLOBINEMIA WARNING"** (these two words in bold print and capital letters as the first statement under the heading "WARNINGS"): Use of this product may cause methemoglobinemia, a rare but serious condition that must be treated promptly because it reduces the amount of oxygen carried in blood. Stop use and seek immediate medical attention if you or a child in your care develops:
 - pale, gray, or blue colored skin (cyanosis)
 - headache
 - rapid heart rate
 - shortness of breath
 - dizziness or lightheadedness
 - fatigue or lack of energy

C. Efficacy Data

- i. Supply one copy of all available physical and chemical property information developed in laboratory studies or similar materials that might be predictive of clinical use/behavior.

- ii. Clinical studies for efficacy may not be necessary for products with active ingredients covered by the FDA monograph on OTC Relief of Oral Discomfort.
- iii. For products with active ingredients that are not covered by the FDA Monograph on OTC Relief of Oral Discomfort, efficacy must be demonstrated in two, independent two-week clinical studies utilizing an appropriate placebo control that assess the ability of the product to reduce perceived oral discomfort or pain. Claims of other lengths of time for product effectiveness must be supported by accompanying data. See Appendix for details regarding clinical protocol guidelines.
- iv. A statistically significant reduction in perceived oral discomfort or pain between placebo control and experimental groups is required. This can be evaluated through subject response with a visual analogue scale (VAS) survey pre-/post-treatment or other rating scales for discomfort/pain intensity. Details on how response data is assessed should be outlined in the submitted clinical protocol methodology.

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:

- DiMarco A., Wetmore A., Clinical comparison: Fast-acting and traditional topical dental anesthetic. *Anesth Prog.* 2016 Summer;63(2):55-61.
- Hersh EV., et al. A study of benzocaine gel dosing for toothache. *J Clin Dent.* 2005; 16(4): 103-8.
- Shavit I., et al., A randomized trial to evaluate the effect of two topical anesthetics on pain response during frenotomy in young infants. *Pain medicine.* 2017; 18: 356-362.
- U.S. Food and Drug Administration. Over-the-Counter (OTC) Monograph M022: Oral Healthcare Drug Products for Over-the-Counter Human Use, 2022.
- FDA Drug Safety Communication: Reports of a rare, but serious and potentially fatal adverse effect with the use of over-the-counter (OTC) benzocaine gels and liquids applied to the gums or mouth, April 07, 2011.
- Benzocaine Topical Products: Sprays, Gels and Liquids – Risk of Methemoglobinemia. April 07, 2011.
- 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

Clinical Protocol Guidelines for Oral Discomfort

The following guidelines are provided for the design and conduct of clinical studies to generate evidence for the evaluation of safety and efficacy of topically applied products to the gums or mouth for the temporary relief of oral discomfort. 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.

Study design: Clinical trials should be randomized whenever possible, with participants allocated to treatments through a randomization process. The trials can have a parallel or a crossover design. When using a crossover design, appropriate wash-out periods must be considered for the variables being tested. 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. An attempt should be made to assess the level of compliance of the subjects in the study. Each subject will have a complete oral examination to determine eligibility for the study. 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.

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 or STROBE guidelines, as appropriate, and the checklist should be completed and uploaded with the submission. The Council recommends a minimum of two-week clinical studies to demonstrate the safety and effectiveness of the product.

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. The screening pools should be balanced in test and control groups in terms of gender and age distribution. Participants must be at least 18 years old. The subject populations should be indicative of those for whom the product is intended. Study exclusion criteria should apply to subjects who have a history of diabetes or Methemoglobinemia, poor circulation, insensitive skin, medical histories made remarkable by chronic use of anti-inflammatory, analgesic or psychotropic drugs; are pregnant and/or currently breast feeding; allergies and idiosyncratic responses to product ingredients; eating disorders; periodontal surgery or orthodontic treatment in the preceding three months; teeth or periodontium with pathology or defects likely to cause pain; teeth restored in the preceding three months. Other criteria for inclusion/exclusion of subjects must be provided.

Test product and comparator: For test controls, the clinical study should use a placebo that is identical to the test product except that it does not contain the active ingredient. Acceptance is contingent upon the product demonstrating a statistically significant difference when comparing oral discomfort or pain response from study baseline to endpoint vs. that response for a placebo control.

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.

Assessments for efficacy: Variables assessing efficacy should be clearly described and allow for a comparison between the test product and the comparator. Efficacy shall be demonstrated by achieving a statistically significant reduction of oral discomfort or pain symptoms from baseline to study endpoint in comparison to that of a placebo. Subject response post treatment through VAS or other rating scales for discomfort or pain intensity should be provided.

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 tissues, oral hard tissues, or on dental restorations (e.g. composite resins, porcelain, etc.) must be provided. Observation 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 microorganisms that proliferate and may lead to secondary mucosal lesions. Information submitted for potential effects of new agents in the products shall include assessments of possible toxic effects of these agent(s) or adverse effects of the product formulation. These should include standard toxicological profiles depending on the particular product.

Statistical analysis: Depending on the type of study, 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.

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