

Acceptance Program Guidelines

Products
Used
In the
Management of
Oral Malodor



Council on Scientific Affairs

**Products Used In the
Management of Oral Malodor**

Purpose

The Acceptance Program applies to dental products for which safety and usefulness has been established by biological, laboratory, and/or clinical evaluations where appropriate and where physical standards or specifications do not exist. Accordingly, the purpose of these Guidelines is to provide a structure upon which products used in the management of oral malodor can be considered for ADA Acceptance.

Scope

These guidelines apply to products that are designed to manage oral malodor of non-systemic origin. Oral malodor can be measured in a number of ways, including studies using organoleptic intensity and organoleptic hedonic indices and instruments that quantitate the amount of volatile compounds or bacterial enzymes that contribute to the production of odiferous compounds. While aromatic foods may temporarily contribute to oral malodor, these guidelines are for oral malodor generated by microorganisms or metabolic compounds that reside on teeth, tongue or other sites in the oral cavity. Products that manage oral malodor by either active chemical agents (Type 1) or mechanical means (Type 2) will be considered, and should be used as adjuncts to normal oral hygiene procedures. Products, whose claims fall under the scope of other guidelines, must also satisfy those guidelines.

I. SUBMISSION DIRECTIONS

1. General Information

- A Submissions are to be sent to the Council office:
Director, Product Evaluations
American Dental Association
Council on Scientific Affairs
211 East Chicago Avenue
Chicago, Illinois 60611 - 2678
- B Submissions are to be sent in triplicate along with a market sample of the product under evaluation and packaged as marketed. The Council agrees to return the product sample within six 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 typically for 5 years. Renewal of the classification will be considered by the Council upon reapplication by the manufacturer.
- E Products in the Acceptance Program 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 *.

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 listing)
- B Address (to be used in listing)
- C Phone Number (to be used in listing)
- D Fax Number, E-mail address and website 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.
- F Names and qualifications of scientific personnel responsible for formulation and testing of the product in its manufacturing process.
- G Manufacturer information (if different from above)

*4. Summary of submission. Comprehensive summary of all information on safety and effectiveness of the product.

*5. Product Information

- A Name of product (to be used in listing).
- B Evidence¹ of FDA approval to market (e.g. 510(k) letter or premarket approval [PMA] letter).
- C Claims of efficacy and safety
 - (i) Claims for the products in labeling and in advertising shall generally be limited to those related to management of oral malodor although other claims may be permitted if approved by the Council.
 - (ii) Advertisements must avoid disparagement of other products.
 - (iii) The FDA clearance to market must encompass all claims of efficacy.
- D Patent title(s) and patent number(s) relating to the product.

¹ This requirement may be waived by the Council during the evaluation period. Evidence of approval must be provided prior to use of the ADA Seal.

E Product description

- (i) List the composition or the materials used in the formulation of the product.
- (ii) Principles of design (if applicable)
- (iii) The most likely mechanism of action of the product should be given, with supporting data.

F Labeling

The following caution statement shall appear on the product container: "Persistent oral malodor (bad breath) may indicate a serious underlying disease. If your bad breath persists after three weeks of product usage please consult your dentist or physician as soon as possible".

G Packaging**H Promotional materials*****6. Quality Control Procedures for the Manufacturing of the product.*****7. Safety Data**

Safety must be determined in a six-month study, and documentation on all safety studies is required. If the submitted product has already been used for plaque and gingivitis control or whose active ingredient is generally recognized as safe (GRAS), the necessary 6 month safety studies for the product may have already been performed or would not be required.

Data supporting Type 1 and Type 2 product safety (including alterations in taste perception) must include a clinical study of oral soft tissues and teeth. Existing data can be submitted for products shown to be safe in previous 6-month studies. For products for which no 6-month data exist, oral flora should be monitored over a six-month period in one appropriately sized clinical study (see Clinical Protocol Guidelines) to determine if development of opportunistic and pathogenic organisms occurs (e.g. *S. aureus*, *Pseudomonas*, *E. coli*, yeasts, etc.). Information must be submitted on the biocompatibility of the active agents using the appropriate standards.

A Effect on oral soft tissues (Type 1 and Type 2).

- (i) Gingivitis. Since some chemical agents may cause an increase in pathogenic organisms, gingival inflammation should be assessed with an appropriate index, e.g. Loe and Silness.² Justification for the particular index must be provided.
- (ii) Oral soft tissues. Evidence should be provided that the product does not adversely affect oral soft tissues, including staining. Subjects should be examined in the course of the study for the presence of pathologic conditions such as allergic reaction, oral ulceration, candidiasis, or secondary infections of the oral mucosa that may be manifestations of the proliferation of opportunistic microorganisms.

B Effect on hard tissues and restorative materials (Type 1 and Type 2).

Evidence of lack of effect of products on hard tissues and restorative materials should be provided. Effects may include staining, shade alterations, and loss of structure. An appropriate test for loss of

² Loe, H., Silness, J. Acta Odont. Scand. 21:533-551, 1963

structure would be dependent on the type of chemical agent used. Examples may include but are not limited to solubility and surface examination (i.e. loss of surface gloss, surface roughness, etc.).

C Toxicology (Type 1 and Type 2).

Information submitted for products containing chemical 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. Data on the mutagenicity and the carcinogenicity of the product or its active agents must be submitted.

D Patient perceived adverse effects (Type 1 and Type 2).

Data should be provided on the effect of the product, if any, regarding patient reports of changes in taste, changes in saliva flow, burning sensation, xerostomia, or other characteristics that may be unique to the product.

E Microbiology (Type 1 and Type 2).

Evidence of any shifts in oral flora should be provided from at least one six-month study for products for which no data exists. Oral flora should be monitored in subjects during the study for the development of opportunistic and pathogenic organisms. Data should be obtained at baseline, three weeks and six months. Evidence must be provided that significant detrimental shifts in a representative sample of oral flora have not occurred.

8 Efficacy Data

Product efficacy must be demonstrated *in vivo* by two independent, well-designed, three-week crossover or parallel group design clinical studies utilizing at least one appropriate placebo control. Products that demonstrate effectiveness in shorter time periods (e.g. a few hours) should be evaluated during that time period as well as at three weeks to demonstrate continued effectiveness and safety. All published studies assessing the effectiveness of the product in controlling oral malodor must be referenced, including those that do not show an effect. Studies should be double-blinded if possible. Populations studied should be individuals who have intrinsic oral malodor of oral origin and include individuals from 21 to 65 years of age. The population should include individuals with slight to strong oral malodor. The average organoleptic intensity rating (see Table in Clinical Protocol Guidelines) of the population should be at least 2 ± 0.5 (mild malodor) on an intensity scale of 0-5, or a similar level on other appropriate scales. Studies of products for which specific claims are made must utilize appropriate populations. All treatment groups must be reported.

For Type 1 and Type 2 products for which no 6-month microbiology data exist, oral flora should be monitored over a 6-month period (see Clinical Protocol Guidelines) in one appropriately sized clinical study to determine if microbial resistance develops.

Odor judges used in clinical studies should be calibrated and standardized using a range of standard odorants sufficient to reflect the different patterns of nose receptors. Examples of standard odorants for this purpose would include dimethyldisulfide, indole, cadaverine, butyric acid, and trimethylamine. Different set concentrations of each pure compound in water can be used to give the range of 0-5 for each odor. For hedonic judges appropriate hedonic training should be conducted using appropriate odorants.

- A Depending on the claims being made, oral malodor measurements should be performed at a minimum of two appropriate time periods after baseline during the three-week test period. Additional appropriate measurements should be obtained based on product claims. For example, an overnight product should be assessed at day 2 (at a minimum).
- B Significant reductions in oral malodor from baseline to a subsequent time point (See 8.a.) for the test product vs. the placebo control should be demonstrated.
- C In the clinical evaluations, 80% of the subjects shall demonstrate a reduction to a 0 or 1 rating based on a 0-5 organoleptic intensity rating (see Table in Clinical Protocol Guidelines) or the appropriate matching level on another scale.
- D The mechanism of action should be given (if known), along with supporting data.
- E Microbiology - Evidence should be provided from a 6-month clinical study that development of microbial resistance does not occur.

***9. Comprehensive bibliography**

***10. Copies of most significant articles**

***11. Appendices** – Detailed description of test evaluation methods and any other defined areas.

IV STATEMENT TO BE USED FOR PRODUCTS CLASSIFIED UNDER THESE GUIDELINES.

The content of these statements will be determined by the specific claims justifiable by the data as evaluated by the Council.

V 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.

1. Bosy, A., Kulami, G. V., Rosenberg, M., McCulloch, C.A.G. Relationship of oral malodor to periodontitis: evidence of independence in discrete subpopulations. *J. Periodontol.* 1994; 65:37-46.
2. DeBoever, E.H., Loesche, W.J. Assessing the contribution of anerobic microflora of the tongue to oral malodor. *J. Amer. Dent. Assoc.* 1995;126:1384-1393.
3. Grigor, J., Roberts, A. J. Reduction in the levels of oral malodour precursors by hydrogen peroxide; in vitro and in vivo assessment. *J. Clin. Dent.* 1992;3:111-115.
4. Kostelc, J.G., Preti, G., Zelson, P.R., Brauner, L., Baehn, P. Oral odors in early experimental gingivitis. *J. Periodont. Res.* 1984;19:303-312.
5. Kozlovsky, A., Gordon, D., Gelernter, I., Loesche, W.J., Rosenberg, M. Correlation between the BANA test and oral malodor parameters. *J. Dent. Res.* 1994;73:1036-1042.
6. Kozlovsky, A., Goldberg, S. Natour, I., Rogatky-GAT, A. Gelernter, I., Rosenberg, M. Efficacy of a 2-phase oil: water mouthrinse in controlling oral malodor, gingivitis, and plaque. *J. Periodontol.* 1996;67:577-582.
7. Loe, H., Silness, J. Periodontal disease in pregnancy.I. Prevalence and severity. *Acta Odont. Scand.* 1963;21:533-551.
8. Loesche, W.J. The effects of antimicrobial mouthrinses on oral malodor and their status relative to FDA regulations. *Quintessence Int.* 1999;30:311-318.
9. Niles, N.P., Gaffar, A. Relationship between sensory and instrumental evaluation of oral malodor. *J. Soc. Cosmet. Chem.* 1993,44:101-106.
10. Pitts, G., Brogdon, C., Hu, L., Masurat, T., Pianotti, R., Schumann, P. Mechanism of action of an antiseptic, anti-oral malodor mouthwash. *J. Dent. Res.* 1983; 62: 738-742.
11. Preti, G., Clark, L., Cowart, B.J., Feldman, R.S., Lowry, L.D., Weber, E., Young, L-M. Non-oral etiologies of oral malodor and altered chemosensation. *J. Periodont.* 1992; 63:790-796.
12. Rosenberg, M. Clinical assessment of bad breath; current concepts. *JADA* 1996; 127:475-482.
13. Rosenberg, M. Gelernter, I., Barki, M., Bar-Ness, R. Daylong reduction or oral malodor by a two-phase oil-

- water mouthrinse, as compared to chlorhexidine and placebo rinses. *J. Periodontol.* 1992;63:241-254.
14. Rosenberg, M., McCulloch, C.A. Measurement of oral malodor: current methods and future prospects. *J. Periodontol.* 1992; 63:776-782.
 15. Schmidt, N. F., Missan, S. R., Tarbet, W. J., Cooper, A.D. The correlation between organoleptic mouth-odor ratings and levels of volatile sulfur compounds. *Oral Surg.* 1978;45:560-567.
 16. Solis-Gaffar, M., Fischer, T., and Gaffar, A. Instrumental evaluation of odor produced by specific oral microorganisms. *J. Soc. Cosmet. Chem.* 1979; 30: 241-242.
 17. Schmidt, N.F., Tarbet, W. J. The effect of oral rinses on organoleptic mouth odor rating and levels of volatile sulfur compounds. *Oral Surg.* 1978;45:876-883.
 18. Tonzetich, J. Direct gas chromatographic analysis of sulfur compounds in mouth air man. *Archs. Oral Biol.* 1978;28:309-319.
 19. Tonzetich, J., N., S.K. Reduction of malodour by oral cleansing procedures. *Oral Surg.* 1976;42:172-181.
 20. Turesky, S. Gilmore, N. D. Glickman, I.: Reduced plaque formation by the chloromethyl analogue of vitamin C. *J. Periodontol.* 1970;41:41-43.
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 23. Van Steenberghe, D., Breath malodor. *Curr. Opin. Periodontol.* 1997;4:137-143.
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CLINICAL PROTOCOL GUIDELINES

The following guidelines are given for the design and conduct of clinical studies to assess the safety and effectiveness of oral products for management of oral malodor. Additional information concerning clinical trials and clinical trial reporting can be obtained from the Council's Guidelines for Clinical Trial Protocols. For Type 1 products, in each study, the active product should be compared with an appropriate placebo control, along with regular oral hygiene (brushing and flossing). For Type 2 products, the control should be regular oral hygiene. Manufacturers are encouraged to submit their clinical protocols to the Council prior to the start of clinical studies.

Subject selection: In the design of clinical studies for controlling oral malodor, subjects should be included who have intrinsic malodor of oral origin two or more hours after oral activity (eating, drinking or brushing of teeth). Systemic causes for oral malodor should be excluded by history and examination. Unless claims are being made for a specific subset, subjects with oral diseases, such as advanced periodontitis, frank caries, and mucosal diseases and subjects who smoke or wear oral appliances should also be excluded from the study. Since routine professional cleanings may reduce oral malodor, at least one week should elapse after any prophylaxis. Subjects who do not practice daily oral care should not be included in the studies. Patients on medications that alter oral flora (e.g. antibiotics) should also be excluded. The patients included in the study should meet the criteria given in Section II.8 of the guidelines as graded by each of at least two properly trained and calibrated odor judges for evaluation of mouth air. Other criteria for inclusion/exclusion of subjects may be used if adequate rationale is provided.

Study design: Each subject will have a medical and dental history reviewed and recorded including a complete oral examination, periodontal examination and organoleptic examination³ to determine eligibility for study. If included, additional test information should be collected from each subject. On evaluation days, subjects should also refrain from using products that would affect organoleptic readings (e.g. tobacco products, body lotions, shampoo, perfume, and lip stick). Four hours prior to evaluation of oral malodor, the subjects must abstain from ingestion of food, drinking, and oral hygiene. The following additional data will be recorded:

A Baseline organoleptic intensity rating using a scale such as that given below :

TABLE
Organoleptic Intensity Scale (based on Rosenberg³)

Rating	<u>Odor Intensity</u>
0	Odor cannot be detected
1	Questionable malodor, barely detectable
2	Slight malodor, exceeds the threshold of malodor recognition
3	Malodor is definitely detected
4	Strong malodor
5	Very strong malodor

Other organoleptic intensity or hedonic scales may be used if appropriately justified.

B Gingival health

Indices of gingival health and plaque should be recorded for the Ramjford teeth (at a minimum) at the following time periods: 1) baseline; 2) at the end of test phase (for products with prescribed treatment period); and 3) at each recall period.

³ Rosenberg, M et.al., J.Dent. Res., 70, 1436-40, 1991.

The following additional types of data may be submitted:

- A Measurement of Volatile Sulfur Compounds (VSC) using gas chromatography is recommended if available. Other measurement instruments may be used if satisfactory and reproducible calibration documentation of odor measurement is provided.
- B Measurement of other odiferous compounds using an appropriate measurement device, for which satisfactory and reproducible calibration documentation of odor measurement is provided.

During the experimental period the patient will practice routine oral care and use the product as instructed by the manufacturer. If the manufacturer suggests changes in routine oral care this change must also be incorporated in both active and control groups.

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.

Study duration: The efficacy studies will be conducted for a minimum of 3 weeks using a crossover or parallel design utilizing at least one appropriate control. Safety and microbiological assessments should be continued for 6 months from one clinical effectiveness trial if appropriate. Efficacy measurements will be taken as specified in Section 8. On the days of measurement the patient should use the product only in the morning and measurements should be taken at appropriate times based on product claims. Additional measurements should be performed depending on the claims made for the product. Products should continue to be used (depending on product instructions) for at least three weeks and demonstrate continued effectiveness over that time period.

Assessments

A Safety Assessments

(i) Microbiological Assessment

The objective of the microbial assessment of bacteria is to determine whether there are shifts in the balance of flora that might have an adverse effect on oral tissues. Evidence should be provided from a 6-month clinical study that the development of opportunistic and pathogenic microorganisms (e.g. *S. aureus*, *Pseudomonas*, *E. coli*, yeasts, etc.) does not occur with use of the product.

(ii) Oral Soft Tissue Assessment

a. Gingivitis

Since some chemical agents may cause an increase in pathogenic organisms, gingival inflammation should be assessed at baseline, 3 weeks and at 6 months with an appropriate index, e.g. Loe and Silness.² Justification for the particular index must be provided.

b. Soft tissue

Any changes in the oral mucosal tissues should be recorded.

(iii) Oral Hard Tissue Assessment

Justification should be provided for appropriate tests to determine if there are adverse hard tissue effects (staining, decreased enamel hardness, etc.).

B Efficacy Assessments

(i) Oral malodor Assessment

- a. Organoleptic intensity or hedonic examinations will be performed by at least two properly trained and calibrated odor judges blinded to each other, based on samples obtained from oral air.
- b. Two types of instruments that may be used for detection of volatile compounds are:
 1. Gas chromatography or any validated quantitative analytical method can be used as one of the methods for detection of volatile sulfur compounds.
 2. Portable sulphide monitors such as described by Rosenberg et al¹ may be acceptable if satisfactory and reproducible calibration documentation of odor measurement is provided.
- c. Other instruments may be suitable for measuring other oral malodor compounds, for example, fatty acids, if satisfactory and reproducible calibration documentation of odor measurement is provided.
- d. Statistical Analysis

Analysis should compare the changes from baseline to a subsequent time point between the test product and placebo control, and demonstrate a statistically significant difference (See section 8).

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. If more than two groups are being evaluated appropriate multiple comparison tests should be used.

Basic documentation should include summary statistics of outcomes and potentially important variables, by treatment. In multi-center trials, these should be reported separately for each participating center, as well as for all centers combined.

(ii) Microbiological Assessment

The objective of the microbiological assessment is to determine whether or not there is an increase in microbial resistance in a representative sample of oral malodor microorganisms (i.e. changes in MIC, MBC). Evidence should be provided from a 6 month clinical study that this does not occur with use of this product. Data should be obtained at baseline, three weeks and again at 6 months.



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