

Acceptance Program
Guidelines

Over the Counter Home-Use Tooth Bleaching Products

Council on Scientific Affairs

Over The Counter Home-Use Tooth Bleaching Products

Purpose:

The purpose of these guidelines is to determine the safety and efficacy of home-use tooth bleaching systems available to consumers by retail purchase (over the counter) that involve any ingredient (carbamide peroxide, hydrogen peroxide, or any other bleaching agent) by any process (tray application, dentifrice, or other process) designed for extra-coronal application that increases the lightness of natural teeth by alteration of intrinsic tooth color. Bleaching is defined as the treatment, usually involving an oxidative chemical, that alters the light absorbing and/or light reflecting nature of a material structure, thereby increasing its value (whiteness).

Scope:

These guidelines apply to all over the counter home-use tooth bleaching systems utilizing any bleaching ingredient and any process designed for extra-coronal application which alters intrinsic tooth color in order to improve the esthetic appearance of natural teeth. Dentist-dispensed home-use tooth bleaching products are covered under the Guidelines for Dentist-Dispensed Home-Use Bleaching Products and professionally applied bleaching products are covered under the Guidelines for In-Office Bleaching Products. Products which remove extrinsic stain are covered under the Guidelines for Home-Use Tooth Stain Removal Products.

I. SUBMISSION DIRECTIONS

1. General Information

- A Submissions should 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 should be sent in triplicate along with a market sample of the product (i.e., 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 in 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 valid for three years. Renewal of the classification will be considered by the Council upon request by the manufacturer.
- E Classification of a product under the Acceptance Program is subject to the conditions stated in the contract entitled "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 official list of Accepted Products)

B Address (to be used in listing)

C Phone number (to be used in listing)

D Fax number

E Email address and Internet address (if available)

F Names of owners, officers, and other individuals authorized to furnish information to the Council and represent the firm in dealing with the Council. (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).

G Names and qualifications of scientific personnel responsible for formulation and testing of the product in its manufacturing process.

*4. Summary of Submission

Comprehensive summary of the information submitted on safety and effectiveness of over the counter home-use tooth bleaching materials.

*5. Product Information

A Name of product (to be used in listing)

B Evidence of FDA approval to market,¹ if applicable (e.g., 510 (k) letter, pre-market approval [PMA] letter)

C Claims of efficacy and safety

(i) List of claims of efficacy and safety. All claims of safety and efficacy such as whitening,²

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

²Whitening is defined as the process that results in the material becoming similar in color to a preferred or standard white.

brightening³ and lightening⁴ must be documented, including all claims in advertising and promotional materials.

- (ii) The studies (or parts of studies) that provide documentation for each claim must be identified.
- (iii) Advertisements must avoid disparagement of other tooth bleaching systems.

D Patent title(s) and patent number(s) relating to the product

E Product composition and mode of application

F Instructions including indications and contraindications for use

All instructions for the use of over the counter home-use tooth bleaching systems, including any adjunctive materials (e.g., fluoride gels), should be clearly defined as to method of application, exposure time, frequency of application (e.g. minimum time between treatment regimens), and other related techniques. This recommended procedure for use, as defined in the instructions, is the one that is to be tested in laboratory and clinical evaluations for the purposes of the current guidelines. Any substantial departures from these instructions would represent a different home-use tooth bleaching system and would require separate evaluation.

Instructions shall include the following statement: "It is recommended that you consult your dentist before using this product".

Appropriate cautions should be provided for specific populations, e.g. children, special needs patients.

G Labeling

The concentration of the bleaching agent shall be given on the product container.

H Packaging

I Promotional materials

6 Quality Control Procedures for the Manufacturing of the Product

Describe the quality control procedures applied to the manufacturing of the product. This should include the Quality Control tests used during processing and on the finished product, and assurance that the production methods, documentation, and facilities comply with current applicable good manufacturing procedures.

*7 Laboratory Evaluation

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

The following tests should be conducted on extracted human teeth that have been stored in appropriate media, such as 2% sodium azide, and not subject to any conditions that would alter their general

³Brightening is defined as the process that results in a material appearing to reflect either diffusely or specularly, more light.

⁴Lightening is defined as the process that results in the material reflecting diffusely a greater amount of the incident light.

properties. Most likely the teeth would be extracted third molars, however, they should be erupted for at least a year. Their enamel is considered an acceptable representative of the enamel for the facialsurfaces of anterior teeth, if anterior teeth are not available.

A Enamel hardness testing

Tooth bleaching systems could potentially damage dental enamel or dentin under extreme conditions of use. To insure that no substantial changes in the properties of enamel occur, enamel hardness must be evaluated before and after treatment according to the product's usage instructions. The average Knoop hardness shall be determined by applying a 0.490 N (50 gf) load in accordance with ASTM C 1326. When using this ASTM test method, special attention should be given to the following test parameters: specimen minimum thickness, specimen surface finish, specimen leveling, and spacing of indentations. Furthermore, guidance on the acceptability of indentations shall be adhered to along with the instructions for measurement of indentations. The average Knoop hardness number of ten acceptable indentations before and ten acceptable indentations after treatment shall be compared. These indentations shall be made on the same region on the facial surface of an extracted tooth that has been stored in an appropriate solution, such as 2% sodium azide (note that ASTM C 1326 requirements for minimum spacing of indentations need to be followed). There should be no statistically significant difference in the mean hardness values before and after treatment at the $p < 0.05$ level for a t-test comparison. Test reporting shall comply with the "Report" section of ASTM C 1326.

B Enamel morphology changes

Tooth bleaching systems may potentially produce interactions such as dissolution of prism material. For example, these interactions may produce changes in tooth surface roughness. The bleaching system shall meet the requirements of enamel abrasion in ISO 11609:1995. Evidence must be presented that the treatment does not degrade the surface of the treated enamel and increase its susceptibility to caries demineralization and erosion.

C Restorative material changes

Resin-based and glass-ionomer restorative materials have the potential to experience loss of physical integrity after exposure to bleaching systems. On the other hand, metals and ceramics have a very low potential for reacting with bleaching systems. The verification of physical properties for resin-based and glass ionomer restoratives should be done by comparison of transverse rupture strength 2(TRS) and transverse modulus (TM) before and after exposure to the bleaching system for a period of time simulating clinical use as recommended by the manufacturer. The materials tested should be one brand of microfill composite resin, one conventional glass ionomer cement, and one resin-modified glass ionomer cement. For acceptability, the TRS and TM must not differ between before and after treatment with the bleaching system. The sample dimensions, fabrication methods and test methods from ANSI/ADA Specification No. 27 for Polymer-Based Filling, Restorative, and Luting Materials should be used to determine TRS and TM. Acceptance will be contingent upon achieving statistically similar means of TRS and TM from ten samples tested before and after exposure to the bleaching system. Similarity of means will be verified by t-test at a significance level of $p < 0.05$ and reported as the group means, standard deviations, and p value for the t-test.

D Kinetics of active ingredient release

The release kinetics of active ingredient during the recommended use (i.e., amount of active

ingredient recovered, intraorally, in the bleaching device, on the tooth and in saliva for at least four different time periods) shall be evaluated.

*8 **Toxicological Evaluation**⁵

Products are required to meet the safety requirements detailed in the Guidelines for the Acceptance of Peroxide-Containing Oral Hygiene Products, Council on Dental Therapeutics, American Dental Association, 1994. J Am Dent Assoc (125) 1140-1142.

*9 **Clinical Evaluation**

The following guidelines are for the design and conduct of clinical studies to provide evidence of safety and efficacy. Additional information concerning clinical trials and clinical trial reporting can be obtained from the Council's Guidelines for Clinical Trial Protocols (*See V. References, No. 13*). Manufacturers are encouraged to submit their clinical protocols to the Council for review prior to the start of the clinical studies. The information indicated below is applicable to each independent⁶ clinical study.

The study population should reflect the user population. Safety shall be demonstrated by the absence of irreversible side effects resulting from the use of the product. Human efficacy shall be demonstrated using at least one appropriate system for measuring the change in color.

A Trials

At least two independent double blind clinical trials are required, each at a different site. A placebo control must be used along with the same application method. All sponsored clinical studies evaluating the product in question should be identified at the time of filing.

B Observation times

For those products with a prescribed treatment period, an observation at baseline and within a few days after completion of the treatment regimen is required. For all products, observations are required at 3 months and 6 months following initiation of treatment.

After subject screening, selection and initial instruction the bleaching system will be used for a test period recommended in the instructions for use.

c Subject Selection Criteria

All subjects should have no obvious signs of periodontal disease or untreated dental caries, have at least four maxillary anterior teeth that qualify for the tooth bleaching trial, and be in good physical health with no medical problems that would contraindicate participation in the clinical trial. Subjects should be screened for potential participation in the trial and the screening pool should be examined for balance in terms of gender and broad age distribution. Subjects with dentinal sensitivity should be excluded or the sensitivity should be resolved before the start of the study. Subject population should be indicative of those for whom the product is intended.

⁵ Products that involve 10±1 % tray applied carbamide peroxide as the active agent for which the safety and efficacy has already been established in published research or for which information from clinical trials submitted to the ADA for the Seal program has already been approved will not have to submit the results of this evaluation or the clinical evaluation below. The concentration of other ingredients must be within 10% of the concentration of those ingredients in the Accepted product.

⁶Different sites, different investigators and different populations. One investigation may be conducted by the company's research department.

D Subjects

A typical clinical trial of this type generally involves at least 25 subjects in each group, experimental and control. Any teeth containing restorations that may be exposed to the test agent during the trial, may be excluded because of potential problems or biases caused by the existing restorations.

Subjects should not have participated previously in tooth bleaching trials. Each subject shall receive an oral prophylaxis at least one week prior to the start of the study.

- (i) Teeth per subject: At least four teeth per subject (maxillary central and lateral incisors) will be evaluated.
- (ii) Subject distribution by gender and age: The subject pool should have a relatively even distribution of subjects of both genders (40% to 60% male or female) and should have some representatives of a wide range of ages.

E Color change measurement methods

Changes in color in teeth should be measured using at least one of the following methods: i) color measurement devices such as colorimeters, digital image analyzers or spectrophotometers; or ii) special color matching scales (e.g., porcelain shade guides, custom shade guides). Justification of the evaluation method must be provided. Reliability of the color measurement method must also be assessed.

F Evaluation periods

For each group, teeth must be evaluated in a natural state of hydration before treatment, a few days after completion of treatment (for products with a prescribed treatment period), and at 3 and 6 months post initiation of treatment. Test periods may vary depending on the nature of the application regime. Reports summarizing the clinical information at all recall periods should be submitted for the following time periods for review.

- (i) Before treatment (0 weeks)
- (ii) A few days after end of treatment
- (iii) 3 months post-initiation of treatment
- (iv) 6 months post-initiation of treatment

G Clinical evaluation procedures and records

Document the procedures, methods of clinical evaluator training for compliance with the procedures, and methods of recording the clinical evaluation data.

- (i) Clinical evaluators: Record the identification of the operator for each clinical evaluation for future reference to consider the potential for operator effects on the evaluations. Whenever possible, the same clinical evaluator should see the same subject during all of the recalls.
 - (a) Evaluator training and retraining (when using shade guides): All evaluators must establish that they meet a minimum of 85% consensus with a standard evaluation scale prior to participation in the clinical trial. Before each recall phase of the clinical trial each evaluator should be calibrated again using the standardized procedure. All of the details of the standardized procedure must be described for any reports and the outcomes of the standardization should be reported. Any examiner failing the standardization procedure may repeat the process until a level of 85% consensus is achieved.
 - (b) Inter-evaluator effects (when using shade guides): For each recall evaluation, the results of the clinical evaluations shall be statistically analyzed ($p \leq 0.05$) by evaluator to determine if any

evaluators are different from the group.

- (c) Intra-evaluator effects (when using shade guides): For the first recall evaluation, the results of the clinical evaluations shall be reported by two clinical evaluators for at least half of allevaluations with at least an 85% consensus of results. This will function to confirm that the standardization procedure is in fact working.
- (ii) Color measurement procedures:
 - (a) Controlled lighting conditions: All measurements should be made under the same documented lighting conditions for each observation period. The lighting conditions should be carefully controlled to guarantee that full spectrum natural light is available for color measurements, that other light is excluded, and that strong absorbers (such as dark colored walls or equipment) are not present that could alter the color being observed.
 - (b) Tooth color record keeping: All of the variables of the tooth color measurement procedures should be recorded. At each tooth color evaluation time, information should be collected on the evaluator(s), time of day, procedures for producing full spectrum natural lighting conditions, methods of excluding other light sources, the operatory location, and date.
- (iii) Periodontal health measurement procedures: Gingivitis and plaque measurements on, at a minimum, the Ramjford teeth, before treatment, a few days after at the end of treatment (for products with prescribed treatment period), and measurements at each recall period should be made, e.g., Loe and Silness Gingival Index, Silness and Loe Plaque Index.
- (iv) Oral tissues: Oral soft and hard tissues must be evaluated for adverse effects at each examination period and these results reported
- (v) Adverse effects: All adverse effects should be reported including altered oral sensations (e.g. burning mouth), altered taste, gingival sensitivity, tooth sensitivity, tooth or restoration alteration for each observation period.

10 **Comprehensive bibliography**

A list of appropriate references is attached to this document. Appropriate references should be included to document statements or comparisons made in the report to the ADA Council on Scientific Affairs.

11 **Copies of most significant articles**

In cases in which the color measurement scheme used in the clinical trial is substantially different that the methods of measurement described in this document, then significant articles describing the use, validation, calibration, and controls should be submitted with all reports to the ADA Council on Scientific Affairs.

12 **Appendices**

Detailed descriptions of test evaluation methods and any other defined areas should be included with any reports submitted to the ADA Council on Scientific Affairs.

III. ACCEPTANCE CRITERIA

1. Establishment of safety

Safety shall first be determined by favorable performance of the product in preclinical laboratory tests before clinical trials are initiated (see section 7). Documentation of non-persistent hypersensitivity, gingival health, and adverse effects during all tests in the clinical trial for the time intervals and at the response levels listed below shall be required.

2. Establishment of efficacy

Efficacy shall be determined by favorable performance of the product in laboratory tests and successful documentation of color change in the clinical trials for the time intervals and at the response levels listed below.

A Evaluation periods

Clinical information shall be collected at the times listed below. The percentage of subjects at each recall must be recorded along with the reasons for the subject drop-out. Data must be based on the recall levels as indicated below.

(i) Start of treatment.

(ii) A few days after end of treatment (for products with a prescribed treatment period).

(iii) 3 months post-initiation of treatment.

(iv) 6 months post-initiation of treatment.

B Efficacy levels

The recalled teeth in each independent clinical study must demonstrate clinical evidence equal to or exceeding the following limits:

	Mean Color Change [in color change units (ccu)]
1. Start of treatment	- - -
2. A few days after end of treatment (for products with a prescribed treatment period)	3 ccu
3. 3 months post-initiation of treatment	3 ccu
4. 6 months post-initiation of treatment	3 ccu

3 ccu = either a change of ≥ 3 steps using a 16 step VitaPan Classical value-ordered shade guide or a change of $\geq 3.0 \Delta E^*$ units using the $L^*a^*b^*$ system comparing post-treatment scores to pre-treatment scores. Other shade guides or endpoints may be used but justification and comparison to the 16 step VitaPan Classical shade guide must be provided. The color change must be in the direction of lighter, less yellow shades (higher L^* , lower b^*).

IV. STATEMENT

To be used for products classified under these guidelines including qualifiers.

"The ADA Council on Scientific Affairs Acceptance of (Product Name) is based on its finding that it is safe and effective for helping to whiten natural teeth."

V. REFERENCES

1. Ryge G. Clinical criteria. *Inter Dent J* 1980; 30(4):347-358.
2. Ad Hoc Advisory Committee on Dentinal Hypersensitivity, Council on Dental Therapeutics. Recommendations for evaluating agents for the reduction of dentinal hypersensitivity. *J Am Dent Assoc* 1986; 112:799-800.
3. McCracken MS, Haywood VB. Effects of 10% carbamide peroxide on the subsurface hardness of enamel. *Quintessence Int* 1995; 26:21-24.
4. Baratieri LN, Ritter AV, Jonteiro S Jr, Caldeira de Andrada MA, Vieira LCC. Nonvital tooth bleaching: guidelines for the clinician. *Quintessence Int* 1995; 26:597-608.
5. Croll TP, Sasa IS. Carbamide peroxide bleaching of teeth with dentinogenesis imperfecta discoloration: report of a case. *Quintessence Int* 1995; 26:683-686.
6. Yap AUJ, Bhole S, Tan KBC. Shade match of tooth-colored restorative materials based on a commercial shade guide. *Quintessence Int* 1995; 26:697-702.
7. Myers ML, Dickinson GL, Curtis JW Jr, Russell CM. Evaluating color change following vital tooth bleaching. *J Esthet Dent* 1995; 7:256-262.
8. O'Brien WJ, Boenke KM, Groh CL. Coverage errors of two shade guides. *Int J Prosthodont* 1991; 4:45-50.
9. Schwabacher WB, Goodkind RJ. Three-dimensional color coordinates of natural teeth compared with three shade guides. *J Prosthet Dent* 1990; 64:425-431.
10. Swift Jr EJ, May Jr KN, Wilder Jr AD, Heymann HO, Wilder RS, Bayne SC. Six-month clinical evaluation of a tooth-whitening system using an innovative experimental design. *J Esthet Dent* 1997; 9:265-274.
11. American Dental Association Guidelines for the Acceptance of Peroxide-Containing Oral Hygiene Products. Council on Dental Therapeutics, American Dental Association. *J Am Dent Assoc* 1994; 125:1140-1142.
12. American Society of Testing and Materials Standard C 1326:1999, Standard Test Method for Knoop Indentation Hardness of Advanced Ceramics.
13. ADA Council on Scientific Affairs. ADA Acceptance Program Guidelines for Clinical Trial Protocols. Chicago: American Dental Association, 2003.
14. ANSI/ADA Specification No. 27-1993, Resin Based Filling Materials. Chicago: American Dental Association.



American Dental Association
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Chicago, Illinois 60611-2678