Acceptance Program Guidelines

Products for the Treatment of Dentinal Hypersensitivity

ADA American Dental Association®
Council on Scientific Affairs

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Council on Scientific Affairs

Products for the Treatment of Dentinal Hypersensitivity

Scope:

These guidelines outline criteria used to evaluate products useful in the reduction, elimination or prevention of dentinal hypersensitivity. Products evaluated using these guidelines include toothpastes that contain ingredients which are thought either to obdurate dentinal tubules or to alter the physiologic properties of dentinal fluid, for example. Other product examples would be materials that are applied to affected areas that obdurate dentinal tubules. Products containing fluoride must also satisfy the appropriate Council requirements.

I. SUBMISSION DIRECTIONS

1. General Information

A Submissions are to be sent to the Council Office:
Director, Acceptance Program
Council on Scientific Affairs
American Dental Association
211 East Chicago Avenue
Chicago, Illinois 60611-2678

B Submissions are to be sent both in writing (two copies) and in electronic format (three CDs, indexed to the submission's Table of Contents), along with a market sample of each product under evaluation and packaged as marketed. Products can be evaluated before final packaging is prepared, but final Acceptance will be contingent on review of final packaging.

C Notification of Council action on a submission will vary depending on whether a submission must be reviewed by the Council at one of its meetings, or by an e-mail ballot. The method of review depends on several factors (e.g. the complexity of the submission, the proposed effectiveness claims, etc.). Seal Program staff can advise which method is appropriate for a particular submission. Following are approximate notification times after Council action:

- Council meeting = 2-4 weeks following the Council meeting
- E-mail ballot = 4-6 weeks following receipt of a complete submission

D When a product is classified as "Accepted" (i.e. is awarded the ADA Seal of Acceptance), the Acceptance period is 5 years. Manufacturers will be contacted approximately 6 months prior to expiration of the current Acceptance period to complete the requirements for the next 5 year Acceptance period. Since companies are required to notify the Council prior to making any changes to an Accepted product or to its labeling at any time during the 5 year Acceptance period, the reacceptance process is usually quick, and requires no additional studies*. (*One exception would be if an Acceptance Guideline for the product had been revised during the Acceptance period to require new types of studies. In this case, the company would need to meet the new Guideline criteria for continued Acceptance.)

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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.

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 an asterisk (*).

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

F Names and qualifications of scientific personnel responsible for formulation and testing of the product

***4. Summary of Submission**

A comprehensive summary of the information submitted to support the safety and effectiveness of the product must be provided.

***5. Product Information**

A Name of product (to be used in listing)

B Claims of efficacy

(i) All claims of efficacy, including “reduction of dentinal hypersensitivity” or “control of dentinal hypersensitivity” must be documented. Other examples of claims requiring documentation include “reduces sensitive teeth,” “reduces sensitive roots,” and “controls sensitive teeth.”

(ii) All comparative claims must be supported by two independent clinical studies.

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

D Product description

(i) Chemical composition (if applicable)

(ii) Material safety data sheet (MSDS) or a letter of explanation that an MSDS is not applicable

E Instructions including indications and contraindications for use, precautions, adverse and allergic reactions

F Labelling

G Packaging

H Promotional materials

6. **Quality Control Procedure for the Manufacturing of the Product**

7. **Safety Data**

Studies must be provided to evaluate any effects on oral tissues from use of the product. Data determining the toxicological, carcinogenic, and mutagenic effects of the product and its ingredients must be provided.

*8. **Efficacy Data**

Except for products with 5% KNO_3 active agent or products whose effectiveness is due to obturation of dentinal tubules, companies should submit at least two clinical studies* of similar design, conducted at different sites (where at least one site is not under direct control of the sponsoring study), by different investigators and using different study subjects and an appropriate control.** "Direct control" does not prohibit monitoring of the investigation by the company for legitimate business purposes, as long as such monitoring does not interfere with the scientific autonomy of the investigators.

For 5% KNO_3 products, only laboratory evidence of potassium and nitrate availability and release is required.

For products whose effectiveness is due to obturation of dentinal tubules one double-blind clinical study is required. In addition to the clinical study, a quantitative in-vitro study showing statistically significant evidence of effectiveness of the complete product, compared to a negative control, must be provided. For example, laboratory studies demonstrating that the product is effective in reducing the hydraulic conductance of patent dentinal tubules should be submitted.

All published studies showing the effectiveness of the active ingredient must be referenced, including studies that do not show any effect. All proprietary studies, including those that do not show any effect, must also be provided.

A 20% statistically significant reduction in sensitivity between control and experimental groups for one appropriate stimulus*** is required in both clinical trials. For any additional stimuli used (for example, temperature in addition to tactile) the only requirement is that there be a statistically significant effect favoring the treatment group. Subjects should be tested at least twice at each measurement period to determine their response to pain stimuli and the responses must be within a reasonable range of one another (± 20%).

*9. **Comprehensive Bibliography**

All publications referred to in the previous sections should be listed here.

10. **Copies of the Most Significant Articles**

The published articles which are of pivotal importance for the establishment of safety and effectiveness should appear here.

11. **Appendices**

Detailed descriptions of test evaluation methods and other defined areas should appear here. Copies of reports on the proceedings of conferences, symposia and individual articles detailing study design and statistical analysis should be among the material appended.

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*double blind when possible
**as defined in this guideline
***see *Clinical Test Protocols*, Section III (American Dental Association, 2007)

III. STATEMENTS TO BE USED FOR PRODUCTS CLASSIFIED UNDER THESE GUIDELINES INCLUDING QUALIFIERS:

There will be three possible Seal statements to be used with an Accepted product, depending on the kind of product and whether it contains fluoride. If none of the statements below apply to the Accepted product, a statement will be developed by the Council.

Statement 1: Non-fluoride desensitizing dentifrice
The ADA Council on Scientific Affairs' Acceptance of (Product Name) is based on its finding that the product is effective in helping to relieve sensitivity in otherwise normal teeth, when used as directed.

***Statement 2: Fluoride desensitizing dentifrice**
The ADA Council on Scientific Affairs' Acceptance of (Product Name) is based on its finding that the product is effective in helping to prevent and reduce tooth decay, and to relieve sensitivity in otherwise normal teeth, when used as directed.

***Statement 3: 0.4% stannous fluoride gel making a hypersensitivity claim**
The ADA Council on Scientific Affairs' Acceptance of (Product Name) is based on its finding that the product is effective in helping to prevent and reduce tooth decay, and to relieve sensitivity in otherwise normal teeth, when used as directed.

*Note: Products must have also satisfied the Council requirements for fluoride-containing products

IV. CLINICAL TEST PROTOCOL

Additional information concerning clinical trials and clinical trial reporting can be obtained from the Council's Guidelines for Clinical Trial Protocols (see V. References). Manufacturers are encouraged to submit their clinical protocols to the Council for review prior to the start of clinical studies.

I. **Intended Use of the Product in the Study**

II. **Controls for Use as a Basis for Comparison**
A negative control should be used in clinical studies determining the effectiveness of a test product. The ingredient thought to be active should be deleted for the formulation to act as the negative control. If the test product is not a formulation, but a single substance, then the product should be compared to another product known to be effective in the reduction or elimination of dentinal hypersensitivity or a negative control known to produce no reduction or elimination of dentinal hypersensitivity.

III. **Study Design and Statistical Analysis Kinds of Stimuli**

Stimulus. The stimulus must be measurable, reproducible and behaviorally predictable. Devices can be used to produce mechanical (tactile), thermal, chemical and electrical stimuli. A tactile stimulus can be achieved using a probe from which the pressure applied to the surface being tested can be measured. The Yeaple Probe are examples of such a device.

A thermal stimulus should have the capacity to produce and measure changes in temperature.

There are at present no chemical substances which offer a reliable, valid, bias-free and versatile stimulus.

An electrical stimulus has been used by means of a dental pulp stethoscope. Controversy does exist over the validity of such a device, however. Some believe that, since an electrical stimulus is unlike any that exists clinically, it should not be used. If this stimulus is used, its use must be justified by the company.

Subject Population. The clinical study must be double-blind, with random selection of subjects using either a parallel or crossover design. Subjects may be admitted over a period of time and must be fully informed of the study's nature. Their consent to submit to the testing must be obtained. A balance of age, sex and baseline pain measurement levels is highly recommended. Reliability of baseline pain measurements must be demonstrated. The sample size should be of sufficient power (ß = .80) at a 95% confidence level.

Exclusion criteria should include the following:

- Previous professional desensitizing treatment
- Subject use of over-the-counter products within the previous six weeks
- Medical histories made remarkable by chronic use of anti-inflammatory, analgesic and psychotropic drugs
- Pregnancy and breast feeding
- Allergies and idiosyncratic responses to product ingredients

- Eating disorders
- Systemic conditions that are etiologic or predisposing to dentinal hypersensitivity
- Excessive dietary or environmental exposure to acids
- 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
- Abutment teeth for fixed or removable prostheses
- Crowned teeth
- Teeth that have extensive restorations and those with restorations extending into the test area

The teeth and sites to be tested should be on the facial surfaces of incisors, cuspids and bicuspids where the cervical regions, i.e., the affected sites, are accessible.

From the time of subject selection until testing begins, a standardized oral hygenic regimen must be employed. No desensitizing products should be used during this period.

Study Duration. The duration of the study is dependent on the kind of agent being tested.

- If the product is hypothesized as being effective at reducing dentinal hypersensitivity, then six to eight weeks are necessary.
- If the product is designed to eliminate dentinal hypersensitivity for a specific period, it would be necessary to test immediately following its application with a follow-up test approximating the period thought to be the duration of effectiveness.
- If the product is designed to prevent dentinal hypersensitivity, periodic testing for one year is necessary.

Application of the Stimulus. A stimulus should be measurable and, therefore, reproducible.

Precise reproducibility of a stimulus requires that there always be a linear transfer of energy to the receptive field such as the pulp or tubule complex. When exact reproducibility is in question, multiple stimulus inductions may be necessary and considered fully in relation to the biologic significance of the study results.

All factors that may physically influence the transfer of energy from the stimulus to the receptor field (coupling with the tooth or the receptor field and variable resistance) and factors that psychophysiologically influence the receptor field locally such as “p” factors in the receptor system or central factors including anticipation, must be controlled to the extent possible during stimulus induction. Failure to control such factors will directly influence the potential level of reproducibility.

Overall, the stimulus should be applied with monotonically increasing or decreasing intensity. To prevent the subject from responding erroneously because of errors of habituation or anticipation, the most appropriate type of application for this stimulus is a randomized presentation with each level presented twice and with catch trials (in which no

stimulus is delivered). Although this approach may not be easily adaptable to most clinical trials, it would be the most precise method for basic laboratory studies.

The interval between various kinds of stimulus applications should be specified and be of sufficient duration to prevent interactions between stimuli.

Measurement of Responses. Research has not identified a physiological index that is unequivocally related to changes in pain sensation and not simply related to stimulus intensity. It is impossible to measure pain by measuring only the physical attributes of the noxious stimulus (intensity, frequency, duration). Pain measurement intrinsically requires the assessment of a subjective parameter. The perception of pain is not always directly proportional to the extent of tissue damage or physical trauma that is produced by a defined stimulus.

The major categories of psychophysical methods for evaluation of pain can be classified as either traditional or contemporary. Traditional methods provide indirect assessment of pain by numerical estimates of detection, pain, or tolerance thresholds. Contemporary methods provide direct assessment of pain strength by expression of pain in units of the subjective intensity. Both methods, if properly used, are acceptable.

To measure pain accurately, investigators must assess the subjective experience of pain, as well as the characteristics of the stimulus producing pain. The necessary criteria for accurate, objective pain measure are as follows:

- Reliability. The procedure yields consistent results with time. Reliability across subjects and between test sessions should be determined.
- Validity. The procedure measures unequivocally a specific dimension of pain.
- Bias-free. The procedure is independent of method bias or patient or investigator response bias.
- Versatility. The procedure is applicable for both laboratory and clinical uses.

Where appropriate, more than one level of stimulus may be applied so as to assess the mathematical relationship of response to defined stimulus.

Psychological and physiological factors that may alter the degree of perception (for example—anticipation) should be controlled to the extent possible by standardization of procedure, training of the subject, demonstration of the stimulus and environmental controls (for example—noise, room temperature) including the “equilibrium” of the patient with the system.

To provide accurate interpretation and analysis of pain response, calibration studies should be conducted on pain assessment techniques so as to define the type of measurement scale that is appropriate. The method of calibration of the stimuli, however, remains open. Some attempt at calibration for each study design would be favorable.

Scales of pain that produce ratio scales permit accurate comparison of pain across different groups of patients and within the same patient.

The interval between various kinds of stimulus application should be specified and be of sufficient duration to prevent interactions between stimuli.

Statistical Analysis. The basis for determining sample sizes must be provided in the protocol and must meet the requirements given previously. Basic documentation should include summary statistics for baseline and outcome data for each treatment group.

Possible technical approaches to statistical analysis include, but are not limited to, analysis of variance or covariance, rank tests, or categorical methods depending primarily on the distribution of dependent variable scores that might be observed in a particular trial. Pooling of sensitivity data by patient as well as stratification of the data is allowed. While the nature of hypersensitivity treatments and the location of teeth and site studies do not lead to a strong expectation of site effects, site-specific analysis may be substituted for pooled analyses as appropriate. However, analysis of separate observations within mouths should appropriately account for lack of independence.

IV. **Information reported**

A Methods and criteria for measurements

B Description of test procedure

C Data records

D Description of each failure

E Methods of analysis of data

F Results of analysis of data

G Conclusions based on data

V. REFERENCES

1. ADA Acceptance Program Guidelines for Clinical Trial Protocols. Chicago: American Dental Association, 2007.
2. Pashley DH, Tay FR, Haywood VB, Collins MA, Drisko CL. Consensus-based Recommendations for the Diagnosis and Management of Dentin Hypersensitivity. Comp.Cont. Education Dent. 2008; 29:1-35.

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