

Acceptance Program Guidelines

Products for the Cessation of Smoking and Use of Smokeless Tobacco

ADA American
Dental
Association®
Council on
Scientific Affairs

2010

Council on Scientific Affairs

Products for the Cessation of Smoking and Use of Smokeless Tobacco

Scope:

These Guidelines cover gums, lozenges and patches with active agents intended to help individuals stop smoking and stop the use of smokeless tobacco products.

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 in triplicate, along with one single-sided copy for duplicating purposes. Three samples of each product from different lots shall be provided. Market samples are preferred. 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 for 5 years. Renewal of the classification will be considered by the Council upon request by the manufacturer.
- E Companies with Accepted products 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 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

Comprehensive summary of the information submitted on safety and effectiveness of the products used for the cessation of smoking or use of smokeless tobacco.

*5. Product Information

- A Name of product (to be used in listing)
- B Claims of efficacy
 - (i) Evidence of FDA approval to market if applicable (e.g., 510 (k) letter, pre-market approval [PMA], NDA).¹
 - (ii) The only efficacy claim that will normally be permitted will be that the product helps stop smoking or the use of smokeless tobacco, depending on the product involved.
 - (iii) Claims that the cessation of tobacco use as a result of using the product prevents, reduces or cures diseases such as periodontitis or oral cancer will not be considered unless adequate clinical studies showing that use of this product does one of these things are submitted. The Council will evaluate such claims on a case by case basis.
 - (iv) Claims that smoking and smokeless tobacco use can exacerbate or lead to disease, such as periodontitis or oral cancer, will be permitted.
 - (v) Advertisements must avoid disparagement of other products.

- C Patent title(s) and patent number(s) relating to the product
- D Product description
 - (i) Chemical composition and amounts
- E Instructions including indications and contraindications for use, warnings etc.
- F Labeling/packaging
- G Promotional materials

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

This should include the Quality Control tests used during processing and on the finished product, and assurance that the product meets good manufacturing procedures.

***7. Efficacy Data**

Product efficacy must be demonstrated by two independent, well-designed clinical studies of at least 6 months duration, utilizing a placebo control and conducted by independent investigators.

Studies should assess the ability of a product with an active agent to help individuals stop smoking or use of smokeless tobacco for a 6 month period following cessation of **all** tobacco use. Masked studies are required, uniquely labeled products must be used. At least one study shall be conducted on a US population. Populations selected for the studies must be representative of individuals for whom the product is intended, that is, individuals who use tobacco (e.g. cigarettes, chewing tobacco, and snuff). Trials must report all treatment groups.

All published studies assessing the effectiveness of the product 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.

Measurements of tobacco use should be made at baseline, end-of- treatment, and at 3 and 6 months following cessation of tobacco use.

In order to be awarded the ADA Seal, the following criteria shall be met:

When comparing those who quit all tobacco use in the test and control groups, there should be a statistically significant difference at each post treatment time period in favor of the test group, using a 7 day point prevalence metric.

The most likely mechanism(s) of action of the product should be given, with supporting data.

***8. Safety Data**

For all products:

Information submitted shall include assessments of possible systemic and topical toxic effects of the active agent, using appropriate standard toxicological, mutagenicity and, if agents prove to be mutagenic, carcinogenicity studies.

All adverse reactions, systemic or topical, from the clinical studies, as well as their extent and severity, must be reported.

For products that are administered orally, the following additional information is required from clinical studies in which oral soft tissues and teeth are examined.

A Effect on oral soft tissues

Evidence of the lack of adverse effects on oral soft issues should be provided. Subjects should be examined in the course of the study for the presence of pathologic conditions such as oral ulceration, candidiasis, or other secondary infections of the oral mucosa that may be manifestations of the proliferation of opportunistic or pathogenic microorganisms.

B Effect on teeth

Evidence of the lack of adverse effects on teeth should be provided.

C Other

It is also recommended that data be provided on the effect of the product, if any, on taste sensation, staining of oral tissue, or other characteristics that may be unique to the active formulation.

***9. Comprehensive Bibliography**

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

***11. Appendices**

Detailed description of test evaluation methods and any other defined areas.

III. SEAL STATEMENT TO BE USED FOR PRODUCTS CLASSIFIED UNDER THESE GUIDELINES INCLUDING QUALIFIERS

FOR FDA-APPROVED OTC PRODUCTS DESIGNED FOR SMOKING CESSATION:

"The ADA's Council on Scientific Affairs' Acceptance of [product name] is based on its finding that it can be effective in helping smokers stop smoking, when used as directed. Success is increased when combined with counseling by a dentist or other health care professional."

FOR FDA-APPROVED OTC PRODUCTS DESIGNED FOR SMOKELESS TOBACCO CESSATION:

"The ADA's Council on Scientific Affairs' Acceptance of [Product Name] is based on its finding that it can be effective in helping an individual stop using (specify chewing tobacco or snuff), when used as directed. Success is increased when combined with counseling by a dentist or other health care professional."

IV. 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.

- A Acceptance Program Guidelines for Chemotherapeutic Products for Control of Gingivitis, Council on Scientific Affairs, American Dental Association, 2008.
- B Council on Dental Therapeutics Guidelines for Acceptance of Chemotherapeutic Products for the Control of Supragingival Plaque and Gingivitis. *J Am. Dent. Assoc* 1986; 112:529–532.
- C Recommended Revisions to American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for Gingivitis Control. *J Periodont Res* 1994; 29:299–304.
- D Acceptance Program Guidelines for Clinical Trial Protocols, Council on Scientific Affairs, American Dental Association, 2007.
- E Treating Tobacco Use and Dependence, Clinical Practice Guideline 2008 Update, US DHHS, Public Health Service.

CLINICAL PROTOCOL GUIDELINES FOR PRODUCTS USED FOR THE CESSATION OF SMOKING AND USE OF SMOKELESS TOBACCO

The following guidelines are given for the design and conduct of clinical studies for the evaluation of evidence of effectiveness and safety of pharmacologic agents used for the cessation of smoking and smokeless tobacco. Additional information regarding clinical trials and clinical trial reporting can be obtained from the Council's Guidelines for Clinical Trial Protocols (see References for Further Explanation).

The clinical benefit of these products can best be demonstrated by a significant rate of cessation in smoking or use of smokeless tobacco. In each study, the active product should be compared with a placebo control. An attempt should be made to assess the level of compliance of the subjects in the study. Manufacturers are encouraged to submit their clinical protocols to the Council for review prior to the start of clinical studies.

Sample Size

A sufficient number of subjects who are ready to cease tobacco use should be enrolled in the study to ensure that appropriate statistical tests can be performed.

Measurements and Study Duration

Measurements shall include established biochemical markers such as salivary, urinary or serum cotinine levels or expired alveolar carbon monoxide levels. Seven day point prevalence rates will be taken at least at baseline (prior to the study), immediately following treatment, and at 3 and 6 months following cessation of tobacco use. In addition to the above, self reported cessation may also be included. Because individuals may substitute other forms of tobacco for the one being evaluated, all tobacco use should be reported.

Study Design

Each subject will have a complete oral cavity examination to determine eligibility for the study. Studies should be conducted with populations and under conditions that the product is expected to be used. Both males and females should normally participate; the age of the study populations and the levels of smoking or smokeless tobacco use [e.g. number of cigarettes smoked; amount and duration of use of smokeless tobacco] should be representative of those patients for whom the product is intended; 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. Subjects should not be taking other medications which alter smoking or smokeless tobacco habits. Also they should not have taken such medications within one month of initiation of the study. Other criteria for inclusion/exclusion of subjects must be provided. Use of a standardized counseling intervention (across conditions) is acceptable and encouraged. Details of the intervention should be provided (e.g. content overview, number of treatment sessions, time per session, qualifications of staff delivering counseling, etc.).

Statistical Analysis

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.

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

If the trial employs stratified randomization in the design, the analysis should reflect this. The distributions of important prognostic factors should be compared across treatment groups, and statistical adjustment employed where disparities in prognostic variables may have seriously influenced outcome comparisons. In multi-centered trials, the possibility and nature of treatment by center interactions should be examined. Among many possible technical approaches to statistical analysis, analyses of variance or covariance, original categorical analyses, and rank analyses are typically considered. Mention of these approaches by no means precludes use of other techniques as appropriate to the study design and variables employed. The Odds Ratio should be calculated and should show a significant difference in abstinence with product use.

Safety Assessments

A Oral Soft Tissue Assessment

Refer to Section 8 a. Safety assessments shall be made at each measurement period.

B Oral Hard Tissue Assessment

Refer to Section 8 b. Safety assessments shall be made at each measurement period.

c Other

Refer to Section 8 c.

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