

Acceptance Program Guidelines

Sugar Free¹ Chewing Gums² to Help Reduce/Prevent Cavities

¹ Containing little or no fermentable carbohydrates.

² Preparation formed by the combination of a water-insoluble phase, known as gum base, and a water-soluble phase of sweeteners, flavors and sometimes food colors.

ADA American
Dental
Association®
Council on
Scientific Affairs

2010

Council on Scientific Affairs

Sugar Free Chewing Gums to Help Prevent/Reduce Cavities

Scope:

These guidelines apply to the following sugar free gums:

- Those without active/therapeutic anticaries agents similar in performance** to the ADA accepted, clinically tested, standard sugar free chewing gum without active agents;
- Those with active/therapeutic agents*** intended to provide an additional anticaries benefit over that provided by stimulation of saliva through the act of chewing.

** Using the surrogate tests given in these guidelines

***Active/therapeutic anticaries agents include any agents that provide a beneficial effect on any of the factors or processes that cause cavities. Such factors include, but are not limited to, effect on plaque pH, enamel remineralization and demineralization and effect on cariogenic plaque bacteria.

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 a market sample of the product, i.e., packaged as marketed. The Council agrees to return the product sample within 6 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 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 the 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 and e-mail 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 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 in its manufacturing process.

*4. Summary of submission

Comprehensive summary of the information submitted on safety and effectiveness.

*5. Product Information

A Name of product (to be used in listing)

B Claims of efficacy

(i) Effectiveness claims for the product in labeling and in advertising shall be limited to helping to reduce/prevent tooth decay or to factors that have an effect on reducing/preventing tooth decay.

(ii) All claims of efficacy, including all health benefit claims and all claims which imply a health benefit, must be documented.

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

D Product description

(i) Chemical composition and amounts.

(ii) Principles of design.

- E Instructions including indications and contraindications for use, warnings, limitations, etc.
- F Labeling/packaging
- G Promotional Materials

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

***7. Safety Data**

- A Evidence must be provided that the components of the product are safe for use in the oral cavity. Compliance with applicable FDA standards should be provided (where appropriate).
- B Adequate evidence must be provided that the unsupervised use of the product by the average patient will not be harmful to hard and soft tissues, or restorations.
- C For products that contain active chemotherapeutic agents, information must be provided regarding possible toxic effects of the active product and its formulation. In most cases, standard toxicological profiles are sufficient.
- D For products that contain active chemotherapeutic agents, evidence of the effects on oral flora should be provided from at least one study. Oral flora should be monitored in subjects during the study for the development of opportunistic and pathogenic organisms. Evidence shall be provided that oral flora has not been adversely affected.

***8. Efficacy Data**

Required efficacy data depend on whether or not a sugar free gum contains an active/therapeutic agent intended to help reduce cavities.

A Sugar Free Gums Without Active Anticaries Agents:

Clinical caries trials will not be necessary for sugar free chewing gums without active/therapeutic anticaries agents. Instead, the following in vivo salivary flow rate surrogate test, outlined below in (i), in which the gum being submitted is compared to the ADA Accepted, clinically tested standard sugar free gum¹, and which shows no statistically significant difference in performance, is required. Other flavors or formulation changes of a given gum brand shall also undergo the surrogate test outlined below in (i).

However, based on the form and composition of the sugar free chewing gum, the Council may require additional surrogate tests, outlined below in (ii) or (iii). As stated above, the gum being submitted is to be compared in these tests to the ADA Accepted, clinically tested standard sugar free gum¹ and shows no statistically significant difference in performance. Manufacturers are requested to review their chewing gum formulations with the Council before conducting surrogate testing.

Following are examples of protocols that can be used for each of the surrogate tests. For all three tests all participants should be ≥ 18 years of age and in good general health with at least 20 natural teeth and 8 natural

¹ The ADA Accepted clinically tested standard sugar free gum is available for testing purposes from the American Dental Association. Please contact the Director, Acceptance Program for more information.

posterior teeth (excluding molars) and normal salivary flow rates as determined from an unstimulated salivary flow determination. No appliances or dentures should be worn by the subjects and no medications should be taken during the study. Individuals with allergies to chewing gum, history of PKU, gross untreated caries, advanced periodontitis, and temporomandibular joint disorders should be excluded. Other study designs will be considered if an adequate rationale is presented.

- (i) **In vivo salivary flow rate:** A modification of the method of Dawes and Macpherson (1992) is recommended. At least 15 subjects should participate in the study. Subjects should refrain from eating for a least one hour prior to testing (preferably testing will be done early in the morning before eating that day). Subjects should use both the clinically tested gum and the submitted gum with testing conducted at approximately the same time each day. First a five minute collection of unstimulated whole saliva should be collected. Then one sample of stimulated saliva from gum chewing should be obtained after 20 minutes of chewing at their normal pace without talking. Saliva will be collected in a test tube and weighed. Results will be expressed as mL per minute. There should be at least a 48 hr washout period between tests. After the 20 minute chewing period subjects should be surveyed regarding whether they would normally chew the submitted gum for at least 20 minutes if unsupervised. A suitable protocol for this test can be found in Appendix A.
- (ii) **In vivo rate of return of plaque pH following a cariogenic snack:** A modification of the method of Aguirre-Zero, et.al (1993) is recommended. At least 15 subjects should participate in the study. A double-blind, crossover design should be used. Two days before a test the subjects should refrain from all oral hygiene procedures to permit plaque growth for pH determination. Plaque pH measurements should be made in the morning with subjects refraining from all food or drink for at least 6 hours. After the baseline plaque pH has been measured, the subjects should rinse with a 10% sucrose solution for one minute and then the submitted or clinically tested gum should be chewed with plaque pH monitored at 5, 10, 20, 30 and 40 minutes following the sucrose rinse.
- (iii) **In situ remineralization:** While the method of Leach, Lee and Edgar (1989) is recommended, a number of different in situ remineralization models will be considered. The in situ model shall, however, include the formation of a dental biofilm and diet-induced acid challenges to the partially demineralized enamel specimens which remain in the mouth for the duration of the study so that remineralization is occurring under clinically relevant conditions. At least 15 subjects should participate in the study, which should involve a double-blind, crossover design with a one week washout in between. Chewing gum periods should last for two or three weeks depending on the type of in situ model. Gums should be chewed at least several times per day, each time for 20 minutes.

Statistical Analysis

Demographic and baseline information for the study population as well as descriptive statistics will be presented. Results will be statistically analyzed using a mixed model method suitable for a cross-over design. The model will include a random effect for subject and fixed effects for study period and treatment. For subjects assigned to the same treatment sequence, the model will include sequence and subject within a sequence term. The submitted gum will be tested against the clinically tested gum using the following null hypothesis, H_0 : There is no difference between the two gums during the testing period. The H_0 will be tested at the 5% significance level (two sided). All the comparisons to the control (clinically tested) gum will be performed using Dunnett's adjustment.

B Sugar Free Gums that Contain Active/Therapeutic Agents for the Reduction of Cavities

The ADA Guidelines for Participation in the ADA's Seal of Acceptance Program state that, "The company must

provide objective data from clinical and laboratory studies demonstrating safety and effectiveness.”

- (i) If a company wishes to make an anticaries claim for its sugar free gum with one or more active/therapeutic anticaries agents, the Council will require at least two clinical caries studies showing that the gum provides statistically significantly better caries reduction than the ADA Accepted, clinically tested standard sugar free gum, when used in the same clinical study. The ADA does not specify the study design, and it is up to the company to ensure that it is scientifically sound.
- (ii) If a company **only** wishes to make efficacy claims for effects of the active/therapeutic agent short of cavity reduction, (e.g. plaque pH reduction, enhancing remineralization, decreasing demineralization, reducing cariogenic plaque bacteria), then at least one clinical study demonstrating statistically significantly better performance in the selected area compared to the ADA Accepted, clinically tested standard sugar free gum, when used in the same clinical study, must be submitted. The ADA does not specify the study design, and it is up to the company to ensure that it is scientifically sound.

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

***9. Comprehensive Bibliography Concerning the Product**

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

***11. Appendices**

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

IV. SEAL STATEMENTS TO BE USED FOR PRODUCTS ACCEPTED UNDER THESE GUIDELINES

A Sugar Free Gums Without Active Anticaries Agents:

"The ADA Council on Scientific Affairs' Acceptance of (product name) is based on its finding that the physical action of chewing (product name) for 20 minutes after eating, stimulates saliva flow, which helps to prevent cavities by reducing acids and making teeth more resistant to decay."

B Sugar Free Gums that Contain Active/Therapeutic Agents for the Reduction of Cavities

"The ADA Council on Scientific Affairs' Acceptance of (product name) is based on its finding that (the rest of this statement will highlight the additional benefit provided over salivary stimulation alone.)"

V. REFERENCES

1. Aguirre-Zero O, Zero DT, Proskin HM. Effect of chewing Xylitol chewing gum on salivary flow rate and the acidogenic potential of dental plaque. *Caries Res.* 1993; 27:55-59.
2. Dawes C, Macpherson LM. Effects of nine different chewing-gums and lozenges on salivary flow rate and pH. *Caries Res.* 1992; 26:176-82.
3. Jenkins GN, Edgar WM. The effect of daily gum-chewing on salivary flow rates in man. *J. Dent. Res.* 1989; 68:786-790.
4. Jensen ME, Wefel JS. Human plaque pH responses to meals and the effects of chewing gum. *Br. Dent. J.* 1989; 167:204-208.
5. Manning RH, Edgar WM. pH changes in plaque after eating snacks and meals, and their modification by chewing sugared- or sugar-free gum. *Br. Dent. J* 1993; 174:241-244.
6. Park KK, Schemehorn BR, Bolton JW, Stookey GK. The impact of chewing sugarless gum on the acidogenicity of fast-food meals. *Am. J. Dent* 1990; 3:231-235.
7. Manning RH, Edgar WM, Agalamanyi EA. Effects of chewing gums sweetened with sorbitol or a sorbitol/xylitol mixture on the remineralisation of human enamel lesions in situ. *Caries Res.* 1992; 26:104-109.
8. Leach SA, Lee GTR, Edgar WM. Remineralization of artificial caries-like lesions in human enamel in situ by chewing sorbitol gum. *J. Dent. Res.* 1989; 68:1064-1068.
9. Creanor SL, Strang R, Gilmour WH, Foye RH, Brown J, Geddes DAM, Hall AF. The effect of chewing gum use on in situ enamel lesion remineralization. *J. Dent. Res.* 1992; 71:1895-1900.
10. ADA Council on Scientific Affairs. Acceptance Program Guidelines: Clinical Trial Protocols. Chicago: American Dental Association, 2007.

APPENDIX A

SUITABLE SALIVARY FLOW RATE PROTOCOL

Inclusion Criteria

1. Men and women ≥ 18 years of age in good general health
2. Unstimulated whole salivary flow rate ≥ 0.4 ml/min

Exclusion Criteria

1. Use of any medication that may interfere with salivary flow
2. History of allergy to chewing gum
3. History of PKU
4. Gross untreated dental caries
5. History of temporomandibular joint disorder
6. Any significant soft or hard tissue oral pathology
7. Subjects must not be pregnant or nursing
8. Subjects who have participated in any other clinical study within 1 month of study entry or who will concomitantly participate in such a study

Clinical Examination

All subjects will undergo a screening oral examination including a salivary flow determination (5 minute collection period of unstimulated whole saliva) prior to enrollment in this study. Once accepted in the study, subjects will be instructed to present to the testing center without having eaten for at least one hour. The screening examination and test sessions will be conducted at the same time each day preferably in the morning.

Sialometry

Subjects will be given a chewing gum according to the random code and instructed not to spit it out until the conclusion of the collection of saliva. Subjects will be instructed to swallow to remove any saliva present, then to place the gum in their mouth and chew, without talking, at their normal pace, frequency, and force and to expectorate as needed into a funnel inserted into a 50 mL test tube. Subjects will chew for a timed 20 minutes. Tubes will be weighed on a Mettler balance prior to and following collection, the tare weight will be subtracted from the post-collection weight, and the 20 minute flow rate calculated using the conversion of 1.0 gm=1.0 ml. Values will be expressed as mL per minute and recorded in the Salivary Flow Rate Form.

The procedure will be repeated until each of the subjects has tested each of the chewing gums. There will be a 48-72 hour washout period between each test session.

Statistical Methods

No formal sample size calculation was performed for this study. However, based on previously published studies, the sample size of 15 subjects was deemed to be sufficient for the study objective.

Demographic and baseline salivary flow information for the study population as well as descriptive statistics will be presented. Salivary flow rate (ml/min) for the 2 treatments will be statistically analyzed using a mixed model method suitable for a cross-over design. The model will include a random effect for subject and fixed effects for study period and treatment. For subjects assigned to the same treatment sequence, the model will include sequence and subject within a sequence term. The submitted gum will be tested against the clinically tested gum using the following null hypothesis, H_0 : There is no difference in salivary stimulation between the two gums during a 20 minute chew. The H_0 will be tested at the 5% significance level (two sided). All the comparisons to the control (clinically tested) gum will be performed using Dunnett's adjustment.

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