

Subcommittee members. Proof of effectiveness of a single ingredient or combination of ingredients was determined by evaluating data from valid, well-controlled studies demonstrating a significant reduction of the symptoms or a therapeutic benefit for the stated indication in the labeling.

Although the OTC drug review is an active ingredient review, not a product review, the Subcommittee recognizes that a final product must be formulated properly, according to accepted pharmaceutical manufacturing practices. If a product is not formulated properly, active ingredients may be present in less than the minimum effective dose, may be in a form that does not exert the intended therapeutic effect(s), or may not be bioavailable. Therefore, the Subcommittee considered it important whether or not inert ingredients or other active ingredients in a formulation might alter the effect of the product's principal active ingredient. The designation of a pharmaceutical necessity as an inactive ingredient does not necessarily mean that the ingredient is pharmacologically inactive.

The Subcommittee considers its recommended "points to consider" acceptable current approaches for arriving at valid conclusions concerning the effectiveness of OTC antigingivitis/antiplaque drug products. These "points to consider" do not preclude the use of newer, more refined laboratory or clinical techniques to establish effectiveness.

c. Clinical trials. Acceptable studies should state the specific objectives of the study, a review of pertinent literature, and present the scientific rationale for the use of the ingredient. The mode, frequency, and duration of application should be thoroughly described. The indices and variables selected for measuring effectiveness, the methods of measurement, and the rationale for such choices should be characterized. The Subcommittee believes that the effectiveness of an OTC antigingivitis ingredient, antigingivitis/antiplaque ingredient, or ingredient combination should be demonstrated by evidence of a clinically significant endpoint, specifically a reduction and/or prevention of gingivitis. In general, the Subcommittee would also expect a reduction of dental plaque mass and/or plaque virulence (degree of pathogenicity as indicated by the severity of the disease produced). However, the Subcommittee also believes that an ingredient can reduce gingivitis without a demonstrated reduction of plaque. Where possible, additional evidence for the effectiveness

of the agent should be provided by demonstrating a shift in the plaque flora.

i. *Design.* Studies should measure the difference between reduction or prevention of dental plaque and gingivitis resulting from the test ingredient as compared to a placebo. Examples of acceptable experimental designs include crossover, parallel, factorial, sequential, single-blind, and therapeutic equivalency studies. Preference should be given to using double-blind studies with a placebo control. The placebo is the formulation of the test agent without the active ingredient, or some other suitable placebo.

ii. *Subjects.* A sufficient number of subjects should be used to permit statistical analysis for the data obtained. The number of subjects tested should be sufficient to eliminate examiner bias and bias introduced by the placebo effect, if applicable, and to allow for anticipated dropouts and estimated variability of effect. The subjects should be of both genders and within the age groups for which the active ingredient is intended. Specific exclusionary criteria should be given.

iii. *Conduct of the study.* The study should be of sufficient duration to demonstrate effectiveness. The duration will depend upon the actual use, anticipated effect, potential sustained benefits, and any safety considerations. The Subcommittee believes that such studies should be at least 6 months in duration to provide sufficient time for an ingredient to exert an antigingivitis/antiplaque effect and for adverse events to manifest themselves. Six months will also provide time to investigate the possibility that an OTC oral ingredient used daily over an extended period of time might cause a shift in the oral flora that may result in the proliferation of pathogenic microorganisms. Scoring and oral health evaluations should be done at baseline, at completion, and at appropriate intervals during the study. Baseline demographic, medical, historical, and physical data for each subject should be obtained and recorded. Such data should include a medical history, a complete oral examination, laboratory studies, if indicated, and other pertinent data.

The treatments should be performed on a random basis. The randomization procedure should be used so that variables not otherwise controlled balance out. The number and frequency of applications of the preparation should be in accordance with the method outlined in the indication for use and directions in the labeling. The clinical investigative team should

monitor subjects during the study to detect any adverse events and take appropriate action. An evaluation of dose response and possible mechanism of action would enhance any submission.

iv. *Appropriate assessments.* Appropriate assessments using validated or accepted techniques must be used.

v. *Interpretation of data.* Investigative methods should be described in sufficient detail so that experiments can be repeated by another investigator to verify and confirm results. Methods of statistical analysis should be determined before starting the study.

Positive evidence of effectiveness should be obtained from a minimum of two studies, each conducted by an independent investigative group. In addition to statistical significance, clinical importance should be addressed. Strength of effect and concern about statistically significant changes not being clinically significant reflect the importance of randomized controlled trials of longer duration to determine if individuals benefit from proposed agents and interventions. Statistical significance can be easily calculated using a nominal (categorical) scale such as gingival index scores. A large "N" offers scores with an approximately normal distribution so that parametric statistics can be used, as if using exact measures such as in an interval or ratio scale. The gingival index, however, is a nominal scale and the difference between 0 and 2 is not the same as the difference between 1 and 3. Slight differences exist in mean gingival index scores which are not clinically obvious and cannot be easily discerned in a subject. A product can produce a change in the response variable that is statistically significant, yet the question of clinical significance remains unanswered.

III. Classification of Active Ingredients

In addition to carefully reviewing the submitted data, the Subcommittee considered all pertinent data and information available in arriving at its conclusions and recommendations regarding the active ingredients. The following tables summarize the Subcommittee's recommended categorization of active ingredients:

TABLE 2.—CATEGORIZATION OF SINGLE ACTIVE INGREDIENTS

Active Ingredients	Safety	Efficacy
Aloe vera	III	III