

and restored teeth, and abutment teeth, which have been omitted from scoring in these trials. These teeth are among the ones most in need of combating gingivitis.

Because it is the individual who is at risk, it is important to know if each subject has changed. Use of mean gingival index scores for each individual subject is the correct way to calculate the mean score for each trial group at various intervals. However, analysis of each site infers that all sites provide independent observations. This assumes that 100 sites in one subject provide the same outcome information as one site in each of 100 subjects. Differences between subjects are greater than variations within subjects (Ref. 119). The principle noted is "In investigations where experimental units on different levels are employed, use the highest level unit as computational unit" (Ref. 120). All sites within one subject are not at equal risk for gingivitis. Inflammation tends to be more overt at interdental areas than at lingual or facial sites. To quantify the findings (*i.e.*, who and how many in the study groups are affected, and by how much) and to present the findings with appropriate indicators of measurement error or uncertainty (such as confidence intervals), further analyses were completed.

Data from pooled analyses of the eight 6-month studies were presented to the Subcommittee. Results showed that mean index values for men differed between the control and essential oils regimen and were similar to differences seen in women for gingival bleeding, gingival index, and plaque index. Differences in mean values between the control and active agent were presented for subjects aged 18 to 39 years and were similar to differences seen in subjects 40 years old and older. The percent of subjects who improved in bleeding, gingival index, and plaque scores from the initial exam to 6 months was greater in the essential oil group than the control group.

Pooled data from the eight studies were used to compute the odds ratio for reduction in gingival index score. The odds ratio was 4.21 with a 95-percent confidence interval (CI) of 2.79 to 6.36 to achieve a goal of 33 percent reduction in score. The bleeding score odds ratio for all studies where bleeding was assessed was 5.12 (CI 3.29 to 7.97). Again, the target goal was a 33-percent reduction in score. For the reported plaque index score reduction of 33 percent, the pooled (eight studies) odds ratio was calculated at 10.53 (CI 7.06 to 15.71).

The Subcommittee concludes that a combination containing eucalyptol (0.092 percent), menthol (0.042 percent), methyl salicylate (0.060 percent), and thymol (0.064 percent) in a hydroalcoholic vehicle containing 21.6 to 26.9 percent alcohol in a mouthrinse meets the requirements of FDA's policy regarding fixed combinations of OTC active ingredients with the same pharmacological action. The Subcommittee concludes that each of these ingredients contributes to the antibacterial activity of the combination, and that each is safe individually and in combination.

Based on the data submitted, the Subcommittee concludes that the combination of eucalyptol (0.092 percent), menthol (0.042 percent), methyl salicylate (0.060 percent), and thymol (0.064 percent) in a hydroalcoholic vehicle containing 21.6 to 26.9 percent alcohol in a mouthrinse is safe and effective as an OTC antigingivitis/antiplaque agent.

#### *B. Category II Conditions*

None.

#### *C. Category III Conditions*

The available data are insufficient to permit final classification at this time. Data to demonstrate safety and effectiveness as an antigingivitis/antiplaque agent will be required in accordance with the guidelines set forth above (*see* general guidelines on safety and effectiveness in section II.H of this document.)

#### *1. Category III Single Active Ingredients*

Aloe vera  
Dicalcium phosphate dihydrate  
Hydrogen peroxide  
Sanguinaria extract  
Sodium bicarbonate  
Sodium lauryl sulfate  
Zinc citrate

a. *Aloe vera*. The Subcommittee concludes that there are insufficient data to permit final classification of the safety and effectiveness of aloe vera as an OTC antigingivitis/antiplaque ingredient. Aloe vera (known in commerce as Curacao Aloe) is a brownish black, opaque mass with a fractured surface that is uneven, waxy, and somewhat resinous (Ref. 121). Aloe vera is obtained from the parenchyma tissue in the center of the leaf by mechanical or chemical means and is highly variable in its properties. The main constituents are polysaccharides, mainly glucomannans, anthraquinone glycosides, and glycoproteins. Other constituents may include sterols, saponins, and organic acids. Aloe vera is topically applied as an emollient, to

aid in wound healing, and relieve burns (including sunburn), and is used for colonic irrigation. Extracts of aloe vera have been shown to enhance phagocytosis (ingestion by a cell of particulate material, such as microorganisms) in adult bronchial asthma. It is also used as an ingredient in many cosmetic preparations (Ref. 122). Aloe vera is produced by boiling Aloe juice down and pouring the viscous residue into empty spirit cases, in which it is allowed to solidify. Aloe vera possesses a nauseating and bitter taste and a disagreeable, penetrating odor. It is almost entirely soluble in 60 percent alcohol and contains not more than 30 percent of substances insoluble in water. Solutions of aloes gradually undergo change and, after a month, may no longer react normally and may lose the bitterness natural to aloes (Ref. 123).

i. *Safety*. The safety of aloe vera is difficult to discern from the data. However, there are studies in which the toxicity of components of aloe vera are discussed, *e.g.*, the component, acemannan (Ref. 124). Also, there is evidence that application of aloe vera to wounds will delay healing (Refs. 125 and 126). The Subcommittee concludes that the data are insufficient to permit final classification of the safety of aloe vera.

ii. *Effectiveness*. The Subcommittee concludes that there are insufficient data to permit final classification of the effectiveness of aloe vera as an OTC antigingivitis/antiplaque ingredient.

Aloe vera, a plant extract, has been claimed to have antiinflammatory and antiprostaglandin effects, as well as cathartic effects (Ref. 127). There are also claims that aloe vera extract is effective against several gram-positive and gram-negative organisms as well as *C. albicans*. However, the Subcommittee finds that the studies are conflicting and that the concentrations required appear to be 20 percent to 90 percent.

The enzyme blend of protease, lipase, and amylase is described as contributing to 3 percent of the formulation reviewed. There is only a general rationale for use in periodontal disease for debridement resulting in reduction of deposits of hard and soft excretions. However, no valid scientific evaluation of this proposed activity is apparent from the submitted data or from the literature (Ref. 128). In addition, no specific testing of the formulation has been presented or was located in the literature (Ref. 128). Therefore, the Subcommittee concludes that there are insufficient data to permit final classification of the effectiveness of aloe vera as an OTC antigingivitis/antiplaque ingredient.