

ingredients when formulated into a dentifrice.

A 21-day experimental gingivitis study by Saxton and Cummins (Ref. 460) enrolled 37 subjects who were brought to a state of no gingival inflammation following 4 weeks of repeated professional cleaning and oral hygiene instruction. One posterior lower segment of tooth was covered with a vacuum-formed tooth shield as described by Bosman and Powell (Ref. 461). Subjects were instructed not to brush that segment of the tooth, which was covered when the subjects cleaned the remainder of their dentition. The tooth shields also served as carriers for the daily application of the control and test toothpastes. Assessment of inflammation and bleeding was done at baseline and at 3 weeks. Mean scores were significantly lower for the test group at 3 weeks, which was interpreted as the test dentifrice being better in delaying development of gingivitis.

A 12-week motivational brushing trial by Gaare et al. (Ref. 462) included 81 adult subjects described as receiving a prophylaxis and motivation at baseline and then using the combination dentifrice at least twice daily. Plaque index and GI scores improved at 6 weeks; plaque scores continued to improve at 12 weeks; and bleeding scores were maintained at 12 weeks.

A 6-month normal use clinical study by Saxton et al. (Ref. 463) enrolled 268 subjects, with 251 completing the trial. Clinical assessments were made at baseline and at 1, 4, and 6 months. Tooth scaling and polishing were done after baseline assessments, which included plaque index by Loe (Ref. 464), modified gingival index by Lobene (Ref. 112), extrinsic stain indices by Lobene (Ref. 465), supragingival calculus by Volpe (Ref. 466), and gingival bleeding by Ainamo and Bay (Ref. 467). The results at 6 months showed no difference in mean plaque scores and no difference in mean modified gingival index scores. Gingival bleeding was statistically significantly lower for the test group ( $p < 0.01$ ) as was the mean calculus scores ( $p < 0.01$ ). Tooth staining area mean scores were statistically significantly higher ( $p < 0.05$ ) and the stain intensity mean score was also higher ( $p < 0.00$ ) for the test group. It was reported that 17 percent of the test group observed tooth staining for themselves. Tongue staining was clinically detectable in approximately 40 percent of test dentifrice subjects compared to approximately 10 percent of control dentifrice subjects (53 versus 15 subjects at 6 months).

The Subcommittee concludes that the combination of stannous pyrophosphate

(1 percent) and zinc citrate (0.5 percent) in a dentifrice is safe. However, there are insufficient data to permit final classification of its effectiveness as an OTC antigingivitis/antiplaque agent.

#### IV. Analysis of Impacts

FDA seeks specific comment regarding any substantial or significant economic benefit or impact that this proposed rule would have on manufacturers or consumers of antigingivitis/antiplaque drug products. Comments regarding the benefit or impact of this proposed rule on such manufacturers or consumers should be accompanied by appropriate documentation. The agency will evaluate any comments and supporting data that are received and will assess the economic impact of this proposed rule in the preamble to the proposed rule.

#### V. Paperwork Reduction Act of 1995

FDA tentatively concludes that the labeling requirements in this document are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a "public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public" (5 CFR 1320.3(c)(2)).

#### VI. Environmental Impact

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### VII. Request for Comments

The agency is providing interested persons a period of 90 days to submit written or electronic comments to the Dockets Management Branch (see ADDRESSES) regarding this advance notice of proposed rulemaking. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. The agency is also providing interested persons a period of 150 days to submit comments replying to comments regarding this advance notice of

proposed rulemaking. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

#### VIII. References

The following references are on display in the Dockets Management Branch (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Fitzgerald, R. J., and E. G. McDaniel, "Dental Calculus in the Germ-Free Rat," *Archives of Oral Biology*, 2:239–240, 1960.
2. Axelsson, P., and J. Lindhe, "Effect of Controlled Oral Hygiene Procedures on Caries and Periodontal Disease in Adults; Results After 6 Years," *Journal of Clinical Periodontology*, 8:239–248, 1981.
3. Grossi, S. G. et al., "Assessment of Risk for Periodontal Disease: I. Risk Indicators for Attachment Loss," *Journal of Periodontology*, 65(3):260–267, 1994.
4. Emrich, L. J., M. Shlossman, and R. J. Genco, "Periodontal Disease in Non-Insulin-Dependent Diabetes Mellitus," *Journal of Periodontology*, 62:123–131, 1991.
5. OTC Vol. 210642.
6. OTC Vol. 210644.
7. Boring, C. C., T. S. Squires, and T. Tong, "Cancer Statistics 1993," *California Journal of Clinical Cancer*, 43:7–26, 1993.
8. Vincent, R. G., and F. Marchetta, "The Relationship of the Use of Tobacco and Alcohol to Cancer of the Oral Cavity, Pharynx or Larynx," *American Journal of Surgery*, 106:501–505, 1963.
9. Keller, A. Z., and M. Terris, "The Association of Alcohol and Tobacco with Cancer of the Mouth and Pharynx," *American Journal of Public Health*, 55:1578–1588, 1964.
10. Tuyns, A. J., "Oesophageal Cancer in Non-Smoking Drinkers and in Non-Drinking Smokers," *International Journal of Cancer*, 32:443–444, 1983.
11. Smith, E. M., "Epidemiology of Oral and Pharyngeal Cancers in the United States: Review of Recent Literature," *Journal of the National Cancer Institute*, 63(5):1189–1198, 1979.
12. Wynder, E. L. et al., "Oral Cancer and Mouthwash Use," *Journal of the National Cancer Institute*, 70:255–260, 1983.
13. Blot, W. J., "Smoking and Drinking in Relation to Oral and Pharyngeal Cancer," *Cancer Research*, 48:3282–3287, 1988.
14. Graham, S. et al., "Dentition, Diet, Tobacco, and Alcohol in the Epidemiology of Oral Cancer," *Journal of the National Cancer Institute*, 59:1611–1615, 1977.
15. Decker, J., and J. C. Goldstein, "Risk Factors in Head and Neck Cancer," *New England Journal of Medicine*, 306:1151–1155, 1982.
16. Elwood, J. M. et al., "Alcohol, Smoking, Social and Occupational Factors in the Aetiology of Cancer of the Oral Cavity, Pharynx and Larynx," *International Journal of Cancer*, 34:603–612, 1984.
17. Gorsky, M., and S. Silverman, "Denture Wearing and Oral Cancer," *Journal of Prosthetic Dentistry*, 52:164–166, 1984.
18. Winn, D. M. et al., "Diet in the Etiology of Oral and Pharyngeal Cancer Among