

strains and wild-type organisms obtained from saliva sampling. Representative organisms are listed in paragraph F.2.a of this document. Conduct kill-time testing using an exposure time of 30 seconds in the presence of exogenous protein. Use an initial inoculum of 1-percent transmission.

- Demonstrate the *in vivo* activity of the formulation through a short-term experimental gingivitis study of at least 2 weeks duration. A representative protocol, comparing the test product, a clinically tested standard, and a negative control, is included in a submission to the Subcommittee (Ref. 6). The criterion for study validation is statistically significant differences in plaque and gingivitis scores between the clinically tested standard and the negative control. To establish comparability to the standard mouthrinse in this test (or another generally accepted statistical test of clinical comparability), the new mouthrinse formulation must satisfy the "at least as good as" statistical criteria for both plaque and gingivitis scores, i.e., at least statistically significantly comparable or equivalent to the clinically tested standard.

G. Inactive Ingredients

1. Alcohol in Oral Health Care Drug Products

Many OTC mouthrinses contain alcohol (up to 26 percent or more). Concerns were raised when published reports and other information appeared to show a possible risk of developing oropharyngeal cancers from daily use of mouthrinses containing high concentrations of alcohol. After reviewing the available data, the Subcommittee has the following comments concerning high alcohol-content mouthrinses and cancer of the buccal cavity and pharynx (oral).

a. *Oral cancer.* Based on the 1993 statistics for oral cancer in the United States (Ref. 7), the buccal cavity and pharynx are the eighth most common site of cancer, representing approximately 3 percent of all cancers reported. Approximately 30,000 people per year develop oral cancer. The ratio of men to women developing oral cancer is about 2 to 1. The 5-year survival rate for persons with oral cancer is about 33 percent for African-Americans and 50 percent for Caucasians.

Alcohol consumption and tobacco smoking/chewing account for approximately three-fourths of oral cancers in the United States (Refs. 8 through 13). Other less clearly

established causal factors include poor dental conditions, oral infections, nutritional deficiencies, and possibly high alcohol-content mouthrinses (Refs. 14 through 19).

b. *Adverse reactions associated with mouthrinses.* A drug that ordinarily causes no adverse effects with short-term exposure may produce pathologic tissue changes after chronic usage. Prolonged usage of a drug and/or its metabolites combined with various compounds in the mouth may result in cumulative effects in oral tissues. Mouthrinses should be evaluated for chronic, long-term usage and resulting manifestations (Ref. 20).

Mucous membranes of the mouth can absorb mouthrinse ingredients, which may pass systemically into the bloodstream. The literature describes local adverse reactions from mouthrinse usage, ranging in severity from irritancy and sensitization to cancer (Refs. 21, 22, and 23).

Some case-control studies suggest a causal association between mouthrinse use and oral cancer risk, most recently in the largest study to date by the National Cancer Institute (Ref. 24). The cancer risk seems to be greater in females (60 percent) than in males (40 percent) and varies in proportion to dose, tending to increase with increasing duration and frequency of use and the alcohol concentration of the mouthrinse (Ref. 24). Other researchers have found no evidence of an increased cancer risk associated with mouthrinses (Refs. 25, 26, and 27).

The reported risk of oral cancer pertains to mouthrinses with alcohol contents of 25 percent or higher. However, since these mouthrinses also contain other active ingredients, such as essential oils with lipophilic, membranotropic effects, some high alcohol-content mouthrinses may affect tissues by a variety of mechanisms.

Studies that have evaluated the potential for alcohol in mouthrinses to cause cancer have a number of shortcomings: (1) Investigations based on subject accounts without benefit of medical records or other written documentation, (2) unreliable classification of exposure to known risk factors such as alcohol and tobacco in study subjects, (3) lack of consistent dose-response relationships based on frequency and/or duration of mouthrinse use, and (4) combining cases of cancer of the buccal cavity and pharynx despite the fact that mouthrinses are in direct contact only with the mucosa of the buccal cavity.

c. *Alcohol and oral cancer.* Although consumption of alcoholic beverages is a known risk factor for oral cancer, pure

alcohol does not show a direct carcinogenic action in laboratory animals or humans. The cancer associated with alcoholic beverages is probably related to contaminating carcinogens. These include urethane produced from urea reacting with ethyl alcohol during yeast fermentation of fruit juices, and *n*-nitrosamine compounds catalyzed from precursor nitrite and amines, amides, or other nitrosatable agents. Commercial mouthrinses contain distilled ethanol free of these contaminating carcinogens. Other findings suggest an ability of ethanol to enhance the conversion of procarcinogens to mitogens, and of ethanol's metabolite acetaldehyde to produce deoxyribonucleic acid (DNA) abnormalities in human cells.

Animal studies have indicated that ethanol may also function as a cocarcinogen, in association with other substances that are true carcinogens (Ref. 28). Alcohol may act by facilitating the penetration of carcinogens into the mucosa (Refs. 29 through 33). Weak carcinogenic nitrosamines and other compounds have been shown to have enhanced carcinogenicity in the presence of alcohol (Ref. 33). Alcohol may act directly on epithelial cells by altering intracellular metabolism and rendering cells more susceptible to carcinogens (Ref. 28).

Based on these studies, the Subcommittee recommends that further studies on the possible cancer risk associated with high alcohol-content mouthrinses be conducted. These studies should include testing various components of the mouthrinse and pertinent dietary ingredients.

d. *Abuse and misuse of mouthrinses.* Although some OTC mouthrinses contain alcohol, the potential for development of drug tolerance and addiction due to use of these products seems negligible. However, misuse of any mouthrinse product may occur if the product gives the user a false sense of security, diminishing the users's desire to seek professional advice. This problem may be particularly acute for mouthrinses that may subdue signs and symptoms of a gingivitis infection without resolving a more severe, underlying periodontitis infection. A label warning should alert the consumer to this danger.

e. *Alcohol as a facilitator.* While the Subcommittee recognizes that the combination of alcohol and tobacco is associated with a marked increase in the incidence of oral cancer as compared to exposure to tobacco alone, it concludes that the mechanism of this synergism is unknown. Animal studies (Ref. 28) have shown that alcohol has a topical