

harmful or permanent and may be removed by a dentist.”

E. Combination Drug Products

1. General Combination Policy

The Subcommittee recognizes that there may be a reason for combining active ingredients in certain OTC drug products. However, such combinations must be based on a sound and logical scientific rationale. The Subcommittee applied the OTC drug review regulation in § 330.10(a)(4)(iv) in developing a combination policy for antigingivitis/antiplaque drug products. The Subcommittee believes that it is rational to combine oral health care ingredients that meet the regulatory requirements as well as the criteria adopted by the Subcommittee, together with suitable inactive ingredients, provided that: (a) Each active ingredient makes a contribution to the claimed effect, (b) the active ingredients are safe and effective and combining the ingredients does not decrease the effectiveness of any individual ingredient, (c) combining the ingredients does not decrease the safety of the combination compared to a single ingredient, (d) the inactive ingredients are safe and do not interact with or otherwise inhibit the effectiveness of the active ingredients, (e) there is a significant target population that can benefit from the use of the combination, and (f) the combination contains adequate directions for use and is labeled with adequate warnings against unsafe use.

The Subcommittee concludes that the same general principles apply when an active ingredient from a different pharmacological class reviewed by another OTC drug advisory panel is combined with an active ingredient reviewed by this Subcommittee. The rationale for such combinations should be evaluated by FDA according to the combination policy set forth in the reports of both advisory panels and in accordance with the agency's regulations.

2. Criteria for Category I Combination Products

The Subcommittee recommends that each claimed active ingredient in a combination product must make a significant contribution to the claimed effects of the product. Further, two Category I active ingredients from different pharmacological groups may be combined to treat different symptoms concurrently if each Category I active ingredient is present within its established dosage range, the combination is rational, there is a significant target population that suffers

from the concurrent symptoms, and the combination is as safe and as effective as each individual active ingredient used alone.

3. Category I Combination Antigingivitis/Antiplaque Drug Products

The Subcommittee considers it rational to combine antigingivitis/antiplaque agents with an anticaries agent. It is also rational to combine antigingivitis/antiplaque agents with a tooth desensitizing agent. In addition, the Subcommittee considers it rational to combine an antigingivitis/antiplaque agent with an anticaries agent and a tooth desensitizer in a single drug product. Further, the Subcommittee believes that although it has been presented with no scientific basis to recommend the combination of two or more antigingivitis ingredients, two or more antigingivitis/antiplaque ingredients, or combinations of antigingivitis and antigingivitis/antiplaque ingredients, it is theoretically reasonable to combine such ingredients, provided it is demonstrated that each ingredient contributes to the claimed effect and does not decrease the safety or effectiveness of another active ingredient.

F. Testing of Antigingivitis/Antiplaque Drug Products

The Subcommittee concludes that the single active ingredients and the fixed combination of eucalyptol, menthol, methyl salicylate, and thymol placed in Category I have been shown through clinical trials to be safe and effective for OTC use in the control of gingivitis and plaque. However, because product formulation can have a significant impact on the effectiveness of these active ingredients, the Subcommittee recommends that OTC antigingivitis/antiplaque drug products demonstrate their effectiveness through the testing described below. Based on the varying mechanisms of action of the Category I active ingredients, the Subcommittee recommends testing specific to each of the Category I active ingredients to demonstrate their effectiveness in traditional dosage forms (dentifrice, gel, paste, or rinse).

1. Changes in Traditional Dosage Forms

The Subcommittee recommends that drug products containing Category I active ingredients formulated in dosage forms other than those reviewed by the Subcommittee be required to demonstrate antigingivitis/antiplaque effectiveness by a single 6-month, randomized, controlled, clinical trial.

2. Final Formulation Testing

The following testing should be conducted on the product formulation, a standard formulation with effectiveness documented by clinical trials, and a negative control. In general, for a product to be considered effective it must demonstrate that it is statistically substantially equivalent to the standard formulation and statistically superior to the negative control as assessed by reasonable statistical analyses. For validation of the study, the standard must be statistically superior to the negative control. However, during the rulemaking process, the criteria appropriate for these tests should be provided by the product manufacturers.

a. *Cetylpyridinium Chloride Rinse*.

- Determine the *in vitro* antimicrobial activity of the product against representative plaque organisms commonly associated with gingivitis. Representative organisms include, but are not limited to, typed stains of: *Actinomyces viscosus*, *F. nucleatum*, *P. gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, *Candida* species, *S. mutans*, and gram negative enteric rods. Testing to determine a product's *in vitro* antimicrobial activity should include minimal inhibitory concentration (MIC) assays, or 30-second kill-time studies, as appropriate.

- Demonstrate the availability of the active ingredient using a Disk Retention Assay (DRA). A suggested method for this assay is included in a submission to the Subcommittee (Ref. 5).

- Demonstrate the biological activity of the formulation using an *ex vivo* Plaque Glycolysis and Regrowth Model (PGRM). A suggested protocol for this assay is included in a submission to the Subcommittee (Ref. 5).

b. *Stannous Fluoride Dentifrice*.

- An *in vitro* determination of antimicrobial activity against representative plaque organisms commonly associated with gingivitis (described in paragraph F.2.a. of this document) is recommended. Testing to determine a product's *in vitro* antimicrobial activity should include MIC assays, 30-second kill-time studies, or plaque biofilm assays, as appropriate.

- Demonstrate the biological activity of the formulation using *ex vivo* PGRM (protocol for assay, Ref. 5).

c. *Fixed Combination of Eucalyptol (0.092 percent), Menthol (0.042 percent), Methyl Salicylate (0.060 percent), and Thymol (0.064 percent) Rinse*.

- Determine the *in vitro* antimicrobial activity using 30-second kill-time studies with both standard laboratory