

essential to the validity of the investigation and an alternative method of investigation is adequate to substantiate effectiveness. Effectiveness may be corroborated by partially controlled or uncontrolled studies, and reports of significant human experience during marketing. General recognition of effectiveness shall ordinarily be based upon published studies that may be corroborated by unpublished studies and other data.

The characteristics of adequate and well-controlled studies have been developed over a period of years and are described in § 314.126. Studies supporting the safety and effectiveness of OTC drug ingredients should provide sufficient details of study design, conduct, and analysis to allow a critical evaluation of the data in relationship to the above characteristics.

In several proposed and final monographs, the agency has stated that, in order for an active ingredient to be included in an OTC drug monograph, it is necessary that the ingredient be adequately characterized and that these standards be published in an official compendium such as the United States Pharmacopeia (USP) or the National Formulary (NF) (58 FR 28194 at 28284). Such specifications are necessary to assure the identity, strength, quality, and purity of the active ingredient. Therefore, the Subcommittee recommends that a full description of the ingredient, including its physical and chemical characteristics and stability, be provided, and that manufacturers contact and work with the USP to develop monographs for ingredients that are not currently included in that compendium. For ingredients that are currently included in an official compendium, reference to the current edition of the USP or the NF may satisfy this requirement.

a. *Safety.* The Subcommittee's determination of the safety of single ingredients and ingredient combinations is based on the following criteria: (1) The incidence and risk of adverse reactions and significant side effects when the ingredient was used according to adequate directions in the labeling, (2) the margin of safety under conditions of normal use and the potential for harm that might result from abuse or misuse under conditions of widespread OTC availability, (3) the potential for inducing untoward effects on the oral tissues, including irritation, ulceration, inflammation, erosion, and minor effects such as discoloration of the teeth, restorations, and prostheses, etc., and (4) assessment of the benefit-to-risk ratio. The Panel further states that microbial safety should be

determined through clinical evaluation of changes in representative oral microbial populations (e.g., the possible emergence of opportunistic organisms or potential pathogens), in order to assure that there is no adverse change in the balance of the oral microflora under conditions of expected OTC use.

i. *Toxicological studies.* A variety of toxicological data can be obtained to demonstrate that an active ingredient is safe. The Subcommittee recommends that manufacturers conduct the applicable studies discussed below and emphasizes that these recommendations do not preclude the use of alternative comparable methods that are currently available or better methods that may be developed in the future. The Subcommittee recommends that the following data be available for the active ingredient(s) intended for use on the mucous membranes of the mouth and throat.

Testing the effects of various ingredients on animal subpopulations that can reflect human subpopulations should be considered (e.g., hyposalivation studies in nonsalivating animals). Adequate, acceptable, controlled in vivo studies of acute and chronic toxicity in several species of animals should be available. Such studies may include single-dose gavage studies, repeat-dose gavage studies, oral irritation studies, pharmacokinetic/biodistribution studies, and dermal sensitization studies. Information regarding the genetic, reproductive toxicologic, and carcinogenic potential should be considered for ingredients that are going to be used daily on a long-term basis. It is not necessary to determine the LD<sub>50</sub> (lethal dose for 50 percent of the test animals) of the ingredient. However, information about the minimal lethal dose would be useful.

All or some of the recommended toxicological studies may not be necessary for all active ingredients. Some circumstances that might preclude an ingredient from the above testing are: (1) It is already generally recognized as safe, (2) it is a direct food additive, (3) it has been used previously in approved dental drug products, or (4) it is the subject of an OTC drug monograph with a different but similar or related use at a similar concentration and for a similar time period. Published articles may be considered in lieu of the testing recommended above.

One of the Subcommittee's primary concerns regarding antingivitis/antiplaque ingredients is whether or not swallowing the active ingredient presents a threat to the user. The Subcommittee recommends that gavage

studies be used to address concerns about potential systemic toxicity unless applicable published or unpublished studies have been conducted using a dietary admixture mode of administration and comparable toxicokinetics can be shown between gavage and dietary modes of administration. Single administration gavage studies are typically performed using a limit-value test in the rat at a specified high dose to evaluate acute toxicity potential (Refs. 46, 47, and 48). In the absence of adequate dietary admixture studies, repeat dose gavage studies may be employed to evaluate systemic toxicity from multiple exposures. The test article is administered to rats on a number of consecutive days.

Where there is a concern that antingivitis/antiplaque active ingredients may induce untoward effects on the oral mucosa, the dosage to be used for these studies should be justified based on the concentration of human exposure levels. An appropriate dosage range may extend, for example, from a low dose comparable to swallowing a single dose of mouthrinse or the amount remaining following expectoration of a mouthrinse to a high dose that either causes dose-limiting toxicity or is several orders of magnitude greater than the clinical exposure levels. Such studies usually use four applications per day for a period of 28 consecutive days. The oral irritation should include both a negative and a positive control group. All test articles should be applied in an identical manner. A negative control group may consist of animals that are treated with either water or saline, and the positive control is a group of animals that are treated with the solution that is known to cause a minimal degree of irritation without being inhumane to the animals (e.g., 5-percent solution of sodium lauryl sulfate).

The Subcommittee recommends that the study include abraded mucosa in order to determine whether the test ingredient delays or prevents the healing of oral lesions. The parameters to include are any gross observations of changes in the oral tissue, such as sloughing, ulceration, or bleeding. Following the sacrifice of each animal, the histopathology of oral tissues should be examined.

ii. *Studies in older adults.* The Subcommittee is concerned that older adults might be at greater risk for potential systemic toxicity from the use of antingivitis/antiplaque active ingredients. This is of particular concern because of the continually