I. Test Methodology

Detailed Comments

I. Clarifying Comments Relating to Testing Methodology: Test Modifications, Test Framework for Ingredients, and USP Reference Standards

A. Test Modifications

We endorse the Subcommittee's position that flexibility in defining effectiveness testing is important to account for future advances in technology. Indeed, the Subcommittee clearly indicated its intent not to lock the industry into specific methods of effectiveness testing by stating:

> "The Subcommittee considers its recommended 'points to consider' acceptable current approaches for arriving at valid conclusions concerning the effectiveness of OTC antigingivitis/antiplaque drug products. These 'points to consider' do not preclude the use of newer, more refined laboratory or clinical techniques to establish effectiveness." [68FR32246] (emphasis added)

The Subcommittee further concluded in proposed Section 356.92 "Testing of Antigingivitis/Antiplaque Drug Products:"

> "(d) Test modifications. The formulation or mode of administration of certain products may require modification of the testing procedures in this section. In addition, alternative assay methods (including automated procedures) employing the same basic chemistry or microbiology as the methods described in this section may be used...." (emphasis added)

We recommend that the agency generally acknowledge and support an open approach to new validated technologies and test modifications in the preambles of the Tentative Final Monograph (TFM) and the Final Monograph (FM).

However, we do not agree with the statement that "any proposed modification or alternative assay method shall be submitted as a petition [to the monograph]". Rather, we encourage FDA to elaborate the agency's expectations for how new technologies are to be validated in a companion guidance to the Final Monograph and use the field inspections related to GMPs as the means to ensure compliance. Our reasons for this approach are as follows:

- Monograph amendments traditionally have low priority, leading to needless delays.
- The monograph amendment process itself is lengthy and not suitable as a system for reasonably rapid responses to changes in manufacturing processes driven by product development needs.

- A guidance that incorporates a mechanism for companies contemplating new technologies to optionally receive input from FDA on proposed validation protocols prior to initiating changes in testing methods would help facilitate implementation of new technologies that are validated in line with current FDA thinking.
- The inspection process allows a suitable mechanism for companies to be held accountable. It is in the business and product development interests of companies to market effective products. With performance testing in the final monograph as a starting point, a guidance on the expectations of new technology validation, and potentially an opportunity to discuss validation protocols on a timely basis before their institution, field inspections then become a suitable cost-effective and efficient means to facilitate, rather than potentially hinder through unneeded delays, the development of new technologies.

B. Support for the Testing Framework for Proposed GRAS/E Ingredients

In addition, the ANPR recommends a testing framework for each of the active ingredients, cetylpyridinium (CPC), stannous fluoride (SnF), and the essential oil mixture (EOM). For CPC, the ANPR states any one of three tests may be undertaken to ensure the availability of cetylpyridinium chloride, and cites a reasonable analytical standard that products "containing 72 to 76 percent available cetylpyridinium chloride are active in reducing gingivitis and plaque" [68FR32284]. For CPC, a choice of one of the following would be permitted: an antimicrobial assay, the Disk Retention Assay (DRA), or the ex vivo Plaque Glycolysis and Regrowth Model (PGRM). For SnF, the Subcommittee recommended an antimicrobial assay and PGRM; and for EOM a choice of an antimicrobial assay or a short-term (2-week) experimental gingivitis clinical study.

We support this general type of approach of elaborating the options for test methods to ensure the quality of generic products containing monograph OTC ingredients, as this model for quality assurance has been used successfully for anticaries products.

However, we question whether the Subcommittee has appropriately defined the antimicrobial assay as a suitable *sole* tool in qualifying product, and suggest the need for additional input on this aspect of test methods. On the other hand, it has been our experience and understanding that such tests as the DRA, PGRM and short-term experimental model are suitable to qualify a product since they ensure the availability of active ingredients, as proposed by the Subcommittee, and we urge FDA support these methods as stated in the ANPR.

C. USP Reference Standards

We note that FDA has not yet addressed in this rulemaking process the need for USP reference standards in order to facilitate product development under the OTC Review. We consider this an important issue for FDA to consider at this time.

We note that this was a matter of some discussion among FDA, industry and the dental community, represented by the American Dental Association (ADA), as to whether the United States Pharmacopeia (USP) should develop reference standards for fluoride dentifrice formulations [see 53FR22439]. FDA stepped in to coordinate with USP to establish fluoride dentifrice reference standard formulations that would be made available to manufacturers interested in manufacturing fluoride dentifrices. FDA made information concerning these reference standards available on file in the Dockets Management Branch under a specific docket, labeled Biological Testing Procedures for Fluoride Dentifrices.

We recommend that FDA initiate a similar approach sooner rather than later in the monograph development process for antigingivitis/antiplaque products. For fluoride dentifrice formulations this approach has already proven itself as an effective means to ensure quality by final formulation testing of monograph ingredients.