

November 25, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: FDA Docket No. 81N-033P Proposed Monograph on OTC Antigingivitis/Antiplaque Drug Products; 68 Fed. Reg. 32232 (May 29, 2003)

Dear Sir or Madam:

The following comments are submitted by the Joint Oral Care Task Group (the Task Group) of the Consumer Healthcare Products Association¹ (CHPA) and the Cosmetic, Toiletry, and Fragrance Association² (CTFA) with respect to the establishment of a Monograph for OTC Antigingivitis/Antiplaque Drug Products.

The two trade associations formed the Task Group to address regulatory issues affecting oral care products that their members manufacture and distribute.³ The Task Group members manufacture and distribute a variety of products, including dentifrices and mouthwashes.

¹ The Consumer Healthcare Products Association (CHPA) is a national trade association representing manufacturers and distributors of nonprescription or over-the-counter (OTC) medications. Members of CHPA are responsible for over 90 percent of the retail sales of OTC drugs in the United States. In addition, CHPA members manufacture and distribute many cosmetic products and some products that are both drugs and cosmetics.

² The Cosmetic, Toiletry, and Fragrance Association (CTFA) is a national trade association that represents the personal care products industry. It has an active membership of more than 300 companies that manufacture or distribute the vast majority of finished personal care products marketed in the United States, as well as a large number of OTC drug products and products that are both drugs and cosmetics. CTFA also represents approximately 300 associate member companies from related industries, including testing laboratories and manufacturers of raw materials, ingredients (both active and inactive), and packaging materials.

³ The Task Group members are Access Business Group; Church & Dwight Co., Inc.; Colgate-Palmolive Company; GlaxoSmithKline Company; Johnson & Johnson Consumer Products, Inc.; Pfizer Inc; and The Procter & Gamble Company. These comments represent a consensus developed among the Task Group's membership, but do not supercede or preclude comments by individual members.

The Task Group has welcomed the opportunity to be a participant in the rulemaking process for OTC antigingivitis/antiplaque drug products. The Task Group and its members presented data and other information to the Plaque Subcommittee on numerous occasions throughout its deliberations. We believe that the Advance Notice of Proposed Rulemaking (ANPR) is mostly accurate in its representation of the Plaque Subcommittee deliberations. However, there are some sections that we believe are not accurate and other sections in which the Subcommittee's conclusions are inconsistent with established FDA policies. We therefore offer FDA the following recommendations which should bring the monograph into compliance with established FDA policy. Recommendations are offered regarding several areas of the report: drug/cosmetic status of plaque claims; active ingredients in combination; labeling; formulation testing; inactive ingredients and oral cancer; mechanisms of action; and expansion of the monograph to allow for additional dosage forms.

Throughout these comments, the term "antiplaque/antigingivitis" is used to refer broadly to products or ingredients that are effective in reducing plaque, gingivitis, or both. Where reference is intended to refer only to plaque or only to gingivitis, or specifically to refer to both plaque and gingivitis, the text uses that specific terminology.

Table of Contents

1	Executive Summary of CHPA/CTFA Joint Oral Care Task Group Recommendations to the Advance Notice Of Proposed Rulemaking.....	4
2	Products Making Cosmetic Related Plaque Claims Should Be Regulated as Cosmetics.....	7
3	The Recommendations of the Subcommittee Regarding Safe, Effective, and Rational Combinations of Antigingivitis/Antiplaque Ingredients with Other Oral Health Care Ingredients Should be Adopted by FDA.....	9
	3.1 No Legal or Regulatory Constraint Prevents FDA from Following the Subcommittee Recommendations.....	10
	3.2 The Combination Products Recommended by the Subcommittee are Rational and Serve Important Public Health Purposes.....	13
4	Recommendations for Revisions to the Labeling of OTC Antigingivitis and Antigingivitis/Antiplaque Drug Products.....	15
	4.1 The Indications and Uses Should be Revised.....	15
	4.2 The Information In the Proposed Warning Should Be Communicated Differently on The Label.....	23
	4.3 FDA Should Provide Alternative Labeling Options for Antigingivitis/Antiplaque Drug Products.....	29
5	Points To Consider for Testing of OTC Antigingivitis/Antiplaque Products.....	30
	5.1 Final Formulation Testing.....	31
	5.2 Testing Requirements for Category I Active Ingredients Formulated in Dosage Forms Other Than The Reviewed Dosage.....	37
	5.3 Effectiveness Testing Requirements for Reclassification of a Category III Active Ingredient to Category I.....	37
6	Alcohol as an Excipient Has Not Been Shown to be Related to Oral Cancer.....	38
	6.1 There Is No Need to Require Further Studies on Relationship between Alcohol-Containing Mouthwash Products and Oral Cancer.....	38
	6.2 Alcohol-Containing Mouthrinse Products Do Not Affect the Permeability of the Oral Mucosa under Conditions of Normal Product Use.....	42
	6.3 Testing of Individual Mouthrinse Components for Potential Cancer Risk Is Not Necessary.....	43
7	Mechanisms Other than Plaque Mass Reduction that Produce an Antigingivitis Effect.....	44
8	The Monograph Should Permit Any Dosage Form Suitable for Topical Oral Administration.....	46

1 Executive Summary of CHPA/CTFA Joint Oral Care Task Group Recommendations to the Advance Notice of Proposed Rulemaking

Drug/Cosmetic Status of Plaque Claims

- The Task Group requests that FDA recognize the cosmetic regulatory status of products with plaque claims that are qualified by statements relating solely to cosmetic benefits.
- Cosmetic plaque claims are consistent with the statutory definition of a "cosmetic" product for not only "altering the appearance" but also "cleansing, beautifying, [and] promoting attractiveness." 21 U.S.C. 321(i). Oral care products used to promote "oral hygiene" or to "clean" or "freshen" the mouth or teeth are cosmetic products as the inclusion of such cosmetic attributes in the labeling leaves no doubt about the intended use of the product.
- The majority of the Task Group member companies recommend that FDA recognize the status of cosmetic plaque claims when qualified as to their intended use in the context of the labeling. Colgate-Palmolive Company holds a minority position on drug versus cosmetic claims for plaque and will submit under separate cover its response to the docket on this issue.

Safe, Effective and Rational Combinations of Antigingivitis/Antiplaque

Ingredients with Other Oral Health Care Ingredients

- FDA should accept the determination of the Subcommittee that the three combinations of antiplaque/antigingivitis ingredients with other oral health care ingredients are rational and should be included in the monograph as Category I.
- FDA should withdraw its dissent from the Subcommittee recommendations and permit the OTC marketing of these combination oral health care products in accordance with the Subcommittee's recommendations.

Labeling of Antigingivitis and Antiplaque/Antigingivitis Products

- The labeling for OTC antigingivitis/antiplaque drug products should be revised. The Task Group has reviewed the proposed labeling and believes it is in the best interest of the consumer to modify the proposed indications and warnings.
- The **indication/uses** section should be revised so that basic antigingivitis labeling is consistent for all products and should be broadened to allow multiple descriptions of drug effects.
- The **warnings** should be revised to reflect the intent of the Subcommittee report. The Task Group recommends revised language under the warnings section to incorporate consultation with a dentist if the condition does not improve and inclusion of the phrase “See your dentist regularly,” under the other information section of Drug Facts.

Testing of Antigingivitis and Antiplaque/Antigingivitis Products

- FDA should consider issuing a guidance document for final formulation testing of a product containing a Category I active ingredient. This approach will establish a performance standard for final formulation testing and also allow flexibility in specific parameters to accommodate scientific advances over time.
- The guidance should be based on detailed protocols and identification of key elements submitted by individual companies. New or additional final formulation testing methods must be scientifically valid for this purpose.
- FDA should adopt a noninferiority testing standard for final formulation testing which requires the test product to be both statistically significantly superior to the negative control product and statistically noninferior to the reference standard.
- The Agency should adopt a clinical standard for a Category I active ingredient formulated in a dosage form other than the reviewed dosage form that requires only one 6-month, single site, negative-controlled clinical study.

Excipient Ethanol and Oral Cancer

- The Subcommittee's concerns regarding a possible association between excipient ethanol and oral cancer have been adequately addressed and no further research is needed.
- Based on the evidence, alcohol-containing mouthwash products do not adversely affect the permeability of the oral mucosa under conditions of normal use.
- Testing of individual mouthwash components for carcinogenic potential is not necessary given the lack of an association between alcohol-containing mouthwash products and oral cancer.

Mechanisms Other Than Plaque Mass Reduction That Produce an Antigingivitis Effect

- Antigingivitis agents that achieve their therapeutic effect through a plaque mediated mechanism such as reduction of plaque virulence or plaque metabolism should be considered as appropriate OTC drug products.
- Products that are solely antigingivitis agents (products that achieve a gingivitis benefit but do not significantly reduce plaque mass) may be suitable OTC drug products. It is likely that such products could present little risk of masking the signs/symptoms of a more serious disease. However, these products should be evaluated on a case-by-case basis to determine their safety and efficacy.

The Monograph Should Permit Any Dosage Form Suitable for Oral Topical Administration

- FDA should adopt the Subcommittee's recommendations and expand the permitted dosage forms to include any form suitable for oral topical administration.

2 Products Making Cosmetic Related Plaque Claims Should Be Regulated as Cosmetics.

Task Group Position and Recommendation

Anti-plaque claims were not considered by the original FDA advisory panels in the 1970's. In the 1990 request for data, FDA tentatively concluded that anti-plaque claims should not be regarded as cosmetic. In 1994, the Dental Products Panel recommended that products with anti-plaque claims should be considered drugs. The majority of the Task Group disagrees with this position and believes it is inconsistent with the intent of the Federal Food, Drug, and Cosmetic Act (FDC Act).⁴

The majority of the Task Group believes that the OTC Plaque Products Subcommittee departed from the established interpretation of the FDC Act when it voted to recommend that all claims regarding plaque reduction be classified as drug claims, even if they are qualified solely to refer to an unambiguous cosmetic benefit. FDA should reject the Subcommittee's recommendation and recognize that a product with properly qualified cosmetic claims about plaque is a cosmetic and not a drug.

Use of the term "plaque" does not in and of itself cause the product to be a drug. In general, the plaque claim needs to be reviewed in the context of the product's full labeling to determine the intended use of the product. Oral care products making plaque-related claims

⁴ Colgate-Palmolive Company holds a minority position on drug versus cosmetic claims for plaque and will submit under separate cover its response to the docket on this issue.

may provide important drug and/or cosmetic benefits to the consumer. Drug benefits include the treatment and/or prevention of gingivitis. Cosmetic benefits include cleansing of teeth to help promote better mouth odor, mouth feel and dental appearance.

Under the FDC Act, the classification of a product is determined by its “intended use,” which is determined by the claims made for the product. A product is a cosmetic if its antiplaque claims pertain only to cosmetic benefits, and no mention is made of prevention or treatment of disease. For these reasons, the majority of the Task Group disagrees with the Subcommittee’s recommendation that all plaque claims will impart drug status. A broader discussion of the Task Group’s position and the history of these claims is found in [Appendix I](#).

The Task Group requests *de novo* legal consideration of this issue. The Agency acting pursuant to the recommendations of its Chief Counsel is the appropriate authority to resolve the question of the proper legal classification of product claims. Although Subcommittee members are medical and dental experts qualified to make recommendations concerning the safety and effectiveness of OTC drugs, they do not have the experience or expertise to address legal issues such as the drug or cosmetic status of a product within the meaning of the FDC Act. Determinations of this type require an understanding of the essentials of statutory interpretation, court decisions, and longstanding Agency regulatory practice.

In summary, use of the term “plaque” is not a drug claim *per se*, but conveys meaningful benefits to consumers through modifying phrases that describe the “intended use” of the product. Thus, the classification of a product should be determined by its intended use, which is determined by the totality of the product’s labeling.

3 The Recommendations of the Subcommittee Regarding Safe, Effective, and Rational Combinations of Antigingivitis/ Antiplaque Ingredients with Other Oral Health Care Ingredients Should be Adopted by FDA

Task Group Position and Recommendations

As the preamble to the proposed monograph reflects,⁵ based upon existing combination products, all of the available data, and its expert judgment, the Subcommittee recommended the following three types of products combining antiplaque/antigingivitis ingredients with other oral health care ingredients as safe, effective, and rational oral health care combination products:

- (1) An antiplaque/antigingivitis ingredient with an anticaries ingredient.
- (2) An antiplaque/antigingivitis ingredient with a tooth desensitizer ingredient.
- (3) An antiplaque/antigingivitis ingredient with an anticaries ingredient and a tooth desensitizer ingredient.

There is also no legal or regulatory constraint that prevents FDA from adopting this recommendation of the Subcommittee. There is no scientific basis for rejecting the Subcommittee's dental expertise in determining that these combination products are safe, effective, rational, and serve an important public health purpose, and the preamble identifies none.

Accordingly, FDA should permit the OTC marketing of these combination oral health care products in accordance with the Subcommittee's proposed monograph.

⁵ 68 Fed. Reg. at 32232

3.1 No Legal or Regulatory Constraint Prevents FDA from Following the Subcommittee Recommendations

In the preamble to the proposed monograph, FDA explains why it did not accept the Subcommittee recommendations on combination products:

“However, the agency is not aware of any marketing history of such combination products eligible for the OTC drug review, nor were such combinations submitted to the Subcommittee. Therefore, the agency is dissenting from these recommendations at this time.”⁶

The Task Group believes that this represents an erroneous statement both about the products reviewed by the Subcommittee and about FDA legal/regulatory authority and policy.

First, at least five combination oral care drug products were submitted for review by the Subcommittee.⁷ A minimum of four of these -- Mentadent P Toothpaste, Arm & Hammer Dental Care Toothpaste, Arm & Hammer Dental Care Toothpowder, and Viadent Toothpaste -- were for combination antiplaque/antigingivitis and anticaries use.

Second, nothing in the FDC Act, or in the Drug Amendments of 1962 that required the OTC Drug Review, prohibits an FDA determination that new conditions of use -- whether active ingredient combinations, indications, dosage forms, dosage classify OTC drugs by therapeutic category and, for each category, set out procedures according to which advisory panels determine the conditions of use under which products in that strengths, routes of administration, or other conditions of use -- are appropriately included in OTC drug monographs. The governing regulations themselves simply category are safe, effective, and not misbranded. FDA informed every panel that it would have complete freedom to

⁶ Ibid

⁷ 68 Fed. Reg. at 32234-32235.

recommend any conditions of use. Nothing in the regulations restricts the content or scope of an OTC drug monograph.

Nor has any subsequent FDA regulation, compliance policy guide, speech, or any other official FDA document ever taken the position that every condition of use set forth in an OTC drug monograph must be traced and documented to a product that was marketed prior to the beginning of OTC Drug Review. Some FDA compliance personnel have occasionally expressed their personal view that this should be the interpretation, but FDA has never issued any official or formal document taking that position. The single sentence quoted above from the preamble to this proposed monograph is, in fact, the first time that this position has ever appeared in print. As will be documented in detail below, the statement made in this preamble is not consistent with, and is in fact contrary to, numerous actions taken by FDA in the context of other proposed, tentative final, and final monographs under the OTC Drug Review.

FDA has, in the course of the OTC Drug Review, approved numerous new forms, new claims, new dosage levels, and new combinations of active ingredients -- as well as other conditions of use -- consistently and without mention of any regulatory or legal obstacle in doing so. For each one of these decisions, FDA has relied upon the scientific judgment and expertise of the advisory panel in determining whether the new condition of use was supported by sound scientific data and expert medical judgment. FDA explicitly adopted a "substantially indistinguishable" standard to determine that, even though a combination drug product had never been marketed before, because the active ingredients had previously been marketed

separately it was possible to determine that the combination is substantially indistinguishable in all respects relevant to the safety and effectiveness of the product.⁸

There are dozens of examples where new combinations of ingredients, that had never before been used in a marketed product, were endorsed as safe and effective by a panel and then adopted by FDA. A few well-documented examples will be sufficient to demonstrate this point. When a panel recommended, and FDA accepted, several new combinations of cough/cold ingredients that had never been previously marketed,⁹ neither the panel nor FDA thought it even relevant to try to trace back each combination to a previously-marketed product.¹⁰ And when FDA issued Compliance Policy Guide No. 450.300 in 1984, it explicitly recognized in section 2(A) that a panel could properly recommend, and FDA could properly accept, a combination of ingredients that had never previously been marketed.

In early 1983, long after the OTC Drug Review began, a company began marketing a combination anticaries/tooth desensitizer drug. Because one of the ingredients had not yet been placed in Category I, FDA brought a seizure action in court and was successful in having the product declared an illegal new drug. United States v. Articles of Drug ... Promise Toothpaste, 624 F. Supp. 776 (N.D. Ill. 1985), affirmed, 826 F.2d 564 (7th Cir. 1987). Subsequently the ingredient was upgraded to Category I, and in 1991 FDA published an amendment to the applicable tentative final monograph to provide Category I status for an

⁸ Letter from FDA Associate Chief Counsel for Enforcement to Richardson-Merrell, Inc. (September 23, 1977).

⁹ 21 C.F.R. part 341

¹⁰ 53 Fed. Reg. at 30522, 20537.

anticaries/tooth desensitizer combination drug.¹¹ FDA then published an enforcement policy specifically to allow this combination drug to be marketed even before promulgation of the final monograph.¹² If FDA had followed the supposed policy quoted above from the preamble to the antiplaque/antigingivitis proposed monograph, it would have been forced to require an NDA for the anticaries/tooth desensitizer combination product. But neither in that case, nor in numerous other similar cases, did FDA ever announce or implement any such policy. Accordingly, FDA should recognize that the reason given for rejecting the Subcommittee recommendation on the three combination products is erroneous. There never was and is not today any such legal or regulatory constraint.

3.2 The Combination Products Recommended by the Subcommittee are Rational and Serve Important Public Health Purposes

Because there is no legal or regulatory constraint against inclusion of new combination products that have never previously been marketed in a monograph, the question then becomes whether there is a scientific and medical justification for concluding that the three combinations recommended by the Subcommittee are rational from a public health and dental health standpoint, and that each of the ingredients when included in the combination will remain safe and effective.

There can be no question but that the combinations that were determined to be rational by the Subcommittee are in the best interests of public health. The success of fluoride in reducing the impact of dental caries in the United States is one of the truly extraordinary public

¹¹ 56 Fed. Reg. at 48302.

¹² 57 Fed. Reg. at 20114.

health accomplishments of the past century. The importance of reducing plaque and gingivitis in this country remains a high priority for the dental health of the public. And for those with sensitive teeth, use of a tooth desensitizer is equally a matter of personal importance. There is no possible medical, dental, or public policy reason for forcing these products to be sold separately. As noted above, FDA has recognized this already by permitting the combination of an anticaries ingredient with a tooth desensitizer, on an expedited basis. There is no rational basis for permitting that combination but excluding an antiplaque/anticaries ingredient. Nor is there any reason to prevent the combined use of an anticaries ingredient with an antiplaque/antigingivitis ingredient for those people who do not need a tooth desensitizer. The Subcommittee recommended these combinations. FDA has provided no scientific, medical, public health, or other basis for rejecting them.

When FDA authorized the expedited marketing of an anticaries/tooth desensitizer combination, it justified this decision on the basis of the “substantially indistinguishable” standard discussed above. That standard applies here as well. There is no basis for determining an anticaries/tooth desensitizer combination is substantially indistinguishable from the individual active ingredients but the combinations recommended by the Subcommittee are not substantially indistinguishable from the individual active ingredients. Such a distinction would be indefensible. FDA has cited no specific safety or effectiveness concern, and the Subcommittee determined that there is none.

Accordingly, the Task Group recommends that FDA accept the determination of the Subcommittee that the three combinations are rational and should be included in the monograph as Category I. FDA should therefore withdraw its dissent from the Subcommittee

recommendations and should permit the OTC marketing of these combination oral health care products in accordance with the Subcommittee's proposed monograph.

4 Recommendations for Revisions to the Labeling of OTC Antigingivitis and Antigingivitis/Antiplaque Drug Products

Task Group Position and Recommendations

The Task Group has reviewed the proposed labeling and believes it would be in the best interest of consumers to modify the proposed indications and warnings. The **indications** sections should be revised so that the labeling is consistent for all products and broadened to allow multiple descriptions of drug effects. The addition of a few words to the regulation for technical clarification will achieve this goal.

The **warnings** in the Subcommittee's report should be revised to be more consistent with longstanding FDA policy on warnings. As the warnings are currently proposed to be worded, the language could mislead consumers by not conveying appropriate use information. It is important that consumers understand that they should ask their dentist if their condition worsens or does not improve after regular use of the product. In addition, the Task Group recommends inclusion of the phrase "See your dentist regularly," in the other information section of the Drug Facts box.

4.1 The Indications and Uses Should Be Revised

"Indications" on OTC labels are synonymous with the term "uses." Indications are differentiated from the statement of identity by location and content. Indications usually expand on the type of benefits that can be expected from the product. The Subcommittee's recommendations are very restrictive in the types of information that can be conveyed to the

consumer in the “uses” section of the Drug Facts box. The “uses” recommended by the Subcommittee for antigingivitis/antiplaque products are summarized in the following table.

The Subcommittee Recommended Uses			
<i>356.65 (b)(1): For all antigingivitis products.</i>	<i>356.65 (b)(2): For antigingivitis products containing stannous fluoride.</i>	<i>356.65 (b)(3): For all antigingivitis/antiplaque products.</i>	<i>356.66 (b)(10): For fixed combination of essential oils</i>
helps [select one of the following]: <ul style="list-style-type: none"> • control • reduce • prevent 	356.65(b)(1) and/or <ul style="list-style-type: none"> • helps interfere with harmful effects of plaque associated with gingivitis. 	helps [select one of the following] <ul style="list-style-type: none"> • control • reduce • prevent • remove 	one or more of the indications for antigingivitis/antiplaque active ingredients in 356.65(b)(3), or the following: <ul style="list-style-type: none"> • helps [select one of the following]: <ul style="list-style-type: none"> • control • inhibit • kill
[select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 		plaque that leads to [select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 	plaque bacteria that contribute to the development of [select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums

4.1.1 Indications and Uses Should be Broadened to Allow Multiple Descriptions of Drug Effects for Gingivitis

The ANPR recommended that only one of three words -- “control,” “reduce,” or “prevent” -- be permitted to describe the action of antigingivitis/ antiplaque products on “gingivitis” or “gingivitis, an early form of gum disease” or “bleeding gums.” Not only is this recommendation unnecessarily restrictive in the information that could be conveyed to the consumer in the “uses” section of Drug Facts, it is unreasonable because the terms “control,” “reduce,” or “prevent” are not mutually exclusive. For example, a consumer with mild

gingivitis could purchase a product to control or reduce gingivitis and continue to use the same product to prevent future gingivitis. A product that can both reduce and prevent gingivitis should be labeled for both indications. In addition, restriction to one term (“control,” “reduce,” or “prevent”) is not meaningful to consumers who want to control, reduce or prevent their existing gingivitis and also prevent gingivitis in additional areas.

The Task Group recommends that antigingivitis (356.65 (b)(1)), stannous fluoride (356.65 (b)(2)), antigingivitis and antiplaque (356.65 (b)(3)) and the fixed combination of essential oils products (356.66(b)(10)) be permitted to use one *or more* of the statements for gingivitis: “control,” “reduce,” “prevent.” These statements provide consumers with truthful information about a product’s uses, especially if the consumer uses the product for more than one purpose. The Task Group’s recommended changes (bolded) for the gingivitis portion of the indication are as follows:

Task Group Recommended Uses for Gingivitis			
<i>356.65 (b)(1): For all antigingivitis products</i>	<i>356.65 (b)(2): For antigingivitis products containing stannous fluoride.</i>	<i>356.65 (b)(3): For all antigingivitis/antiplaque products.</i>	<i>356.66(b)(10): For fixed combination of essential oils</i>
helps [select one or more of the following]	helps [select one or more of the following]	helps [select one or more of the following]	helps [select one or more of the following]
<ul style="list-style-type: none"> • control • reduce • prevent 	<ul style="list-style-type: none"> • control • reduce • prevent 	<ul style="list-style-type: none"> • control • reduce • prevent 	<ul style="list-style-type: none"> • control • reduce • prevent
[select one or more of the following]			
<ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 	<ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 	<ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 	<ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums

4.1.2 Provision for the Effect of Antigingivitis and Antiplaque Agents on Plaque Should Be Broadened to Allow Multiple Descriptions of Drug Effects

For all products effective in reducing gingivitis and plaque (356.65 (b)(3)) the Subcommittee recommended an indication that the product helps “control,” “reduce,” “prevent” or “remove” plaque that leads to “gingivitis;” “gingivitis, an early form of gum disease;” and/or “bleeding gums.” Thus, an example of the uses or indications of a product containing an antigingivitis and antiplaque ingredient would read, “Helps reduce plaque that leads to gingivitis.” Such an indication/use only communicates a portion of the capabilities of the active ingredients. Ingredients that have been categorized both as antigingivitis and antiplaque have demonstrated effectiveness for both antigingivitis and antiplaque clinical endpoints.

Limiting these products to declaring the benefits of “controlling,” “reducing,” “preventing,” or “removing” plaque that leads to gingivitis fails to communicate established product benefits for these products on gingivitis. Ingredients classified as antigingivitis/antiplaque have demonstrated effectiveness in reducing plaque and reducing gingivitis in subjects with pre-existing gingivitis. This was confirmed by the Subcommittee and these benefits should be permitted to be communicated to consumers.

The Task Group recommends that the labeling in proposed section 356.65 (b)(3) be broadened to include both the antigingivitis and antiplaque benefits of these ingredients. This also applies to the labeling in section 356.65 (b)(2) in that stannous fluoride also showed a benefit for both antigingivitis and the “harmful effects of plaque.” Thus, the indications/uses for all antigingivitis/antiplaque and stannous fluoride products should be revised to show the benefits for gingivitis and plaque as follows:

Task Group Recommended Uses for Plaque	
356.65 (b)(2): For antigingivitis products containing stannous fluoride	356.65 (b)(3): For all antigingivitis/antiplaque products.
helps [select <i>one or more</i> of the following]: <ul style="list-style-type: none"> • control • reduce • prevent [select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 	helps [select <i>one or more</i> of the following]: <ul style="list-style-type: none"> • control • reduce • prevent [select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums
and (optionally)	and (optionally)
helps interfere with the harmful effects of <i>plaque or</i> plaque that leads to [select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums 	helps [select one or more of the following]: <ul style="list-style-type: none"> • control • reduce • prevent • remove <i>plaque or</i> plaque that leads to [select one or more of the following]: <ul style="list-style-type: none"> • gingivitis • gingivitis, an early form of gum disease • bleeding gums

4.1.3 Indications for the Killing of Plaque Bacteria and Antiplaque/Antigingivitis Claims for Fixed Combination of Essential Oils Products Should Not Be Mutually Exclusive

Additional indications relating to the killing of plaque bacteria and antiplaque/antigingivitis claims for the fixed combination of essential oils products should not be mutually exclusive. Proposed Section 356.66(b)(10) does not reflect this point. The fixed combination of essential oils products identified in section 356.26 should be permitted to use the indication in Section 356.65(b)(1), Section 356.65(b)(3) and *optionally* the language in Section 356.66(b)(10).

4.1.4 Summary of Recommendations For Labeling “Uses”

Section 356.65(b)(1) should be the basic monograph indication for all antigingivitis products. Antiplaque/antigingivitis ingredients covered under section 356.65(b)(3) could use the indication in section 356.65(b)(1) or the additional language in section 356.65 (b)(3). Stannous fluoride covered under section 356.65(b)(2) could use the indication in section 356.65(b)(1) or the additional language section 356.65(b)(2). The fixed combination of essential oils identified in section 356.26(b) could use the indication in section 356.65(b)(1), section 356.65(b)(3), and optionally the language in section 356.66(b)(10). These recommendations are added to the proposed regulations below. Additions are bolded, italicized, and underlined.

(b) Indications. The labeling of the product states, under the heading “Uses,” one or more of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this part, may also be used, as provided in Sec. 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) For all antigingivitis **and all antiplaque/antigingivitis** products. The labeling states “[bullet] helps [select one **or more** of the following: ‘control,’ ‘reduce,’ or ‘prevent’] [select one or more of the following: ‘[bullet] gingivitis,’ ‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’].”

(2) For antigingivitis products containing stannous fluoride. The labeling states the indication in paragraph (b)(1) of this section and/or the following: “helps **interfere with harmful effects of plaque**” or “helps interfere with harmful effects of plaque associated with [select one **or more** of the following: ‘[bullet] gingivitis,’ **‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’**].”

(3) For all antigingivitis/antiplaque products. **The labeling states the indication in paragraph (b)(1) of this section and/or the following:** and

optionally “[bullet] helps [select one ***or more*** of the following: ‘control,’ ‘reduce,’ ‘prevent,’ or ‘remove’] plaque ***or plaque*** that leads to [select one or more of the following: ‘[bullet] gingivitis,’ ‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’].”

Sec. 356.66 Labeling of combination drug products.

(b) * * *

(10) For permitted combinations identified in Sec. 356.26(p). The labeling of the product states, under the heading “Uses,” one or more of the indications for antigingivitis/antiplaque active ingredients in Sec. 356.65(b)(3), ***and optionally*** the following: “[bullet] helps [select one ***or more*** of the following: ‘control,’ ‘inhibit,’ or ‘kill’] plaque bacteria that contribute to the development of [select one or more of the following: ‘[bullet] gingivitis,’ ‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’].”

In summary, the Task Group recommends that FDA revise the indications/uses section to read as below. Additions are bolded, underlined, and italicized.

Summary of Task Group Recommendations for Labeling “Uses”*

356.65 (b)(1) For all antigingivitis products	356.65(b)(2) For antigingivitis products containing stannous fluoride	356.65(b)(3) For all antigingivitis/antiplaque products	356.66(b)(10) For permitted combinations	
<p>helps [select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ control ▪ reduce ▪ prevent <p>[Select one or more of the following]</p> <ul style="list-style-type: none"> ▪ gingivitis ▪ gingivitis, an early form of gum disease ▪ bleeding gums 	<p>helps [select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ control ▪ reduce ▪ prevent <p>[Select one or more of the following]</p> <ul style="list-style-type: none"> ▪ gingivitis ▪ gingivitis, an early form of gum disease ▪ bleeding gums 	<p>helps [select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ control ▪ reduce ▪ prevent <p>[Select one or more of the following]</p> <ul style="list-style-type: none"> ▪ <u>gingivitis</u> ▪ <u>gingivitis, an early form of gum disease</u> ▪ <u>bleeding gums</u> 	<p>helps [select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ control ▪ reduce ▪ prevent <p>[Select one or more of the following]</p> <ul style="list-style-type: none"> ▪ <u>gingivitis</u> ▪ <u>gingivitis, an early form of gum disease</u> ▪ <u>bleeding gums</u> 	
	AND/OR	AND(<u>OPTIONALLY</u>)	AND(<u>OPTIONALLY</u>)	
	<p><u>helps interfere with harmful effects of plaque</u></p>	<p>OR</p> <p>helps interfere with harmful effects of plaque associated with</p> <p>[Select one or more of the following]</p> <ul style="list-style-type: none"> ▪ gingivitis ▪ <u>gingivitis, an early form of gum disease</u> ▪ <u>bleeding gums</u> 	<p>OR</p> <p>helps</p> <p>[select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ <u>control</u> ▪ <u>reduce</u> ▪ <u>prevent</u> ▪ <u>remove</u> <p><u>plaque</u></p> <p>[select one or more of the following]</p> <ul style="list-style-type: none"> ▪ gingivitis ▪ gingivitis, an early form of gum disease ▪ bleeding gums 	<p>OR</p> <p>Helps</p> <p>[select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ control ▪ reduce ▪ prevent ▪ remove <p>plaque that leads to</p> <p>[select one or more of the following]</p> <ul style="list-style-type: none"> ▪ gingivitis ▪ gingivitis, an early form of gum disease ▪ bleeding gums
			AND(<u>OPTIONALLY</u>)	
			<p>OR</p> <p><u>helps</u></p> <p>[select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ <u>control</u> ▪ <u>inhibit</u> ▪ <u>kill</u> <p><u>plaque bacteria</u></p>	<p>helps</p> <p>[select one <u>or more</u> of the following]</p> <ul style="list-style-type: none"> ▪ control ▪ inhibit ▪ kill <p>plaque bacteria that contribute to the development of</p> <p>[select one or more of the following]</p> <ul style="list-style-type: none"> ▪ gingivitis ▪ gingivitis, an early form of gum disease ▪ bleeding gums

* Task Group recommended changes are underlined, bolded and italicized

4.2 The Information In The Proposed Warning Should Be Communicated Differently on The Label.

The Subcommittee recommended the following warning for all antigingivitis/antiplaque products:

“Warnings: Stop use and ask a dentist if

- gingivitis, bleeding, or redness persists for more than 2 weeks.
- you have painful or swollen gums, pus from the gum line, loose teeth, or increasing spacing between the teeth. These may be signs or symptoms of periodontitis, a serious form of gum disease.”¹³

The warning language proposed by the Subcommittee should not be included in the monograph because it is inappropriate and inconsistent with longstanding FDA policy on warnings. It could inadvertently mislead consumers to delay needed professional treatment and could result in inappropriate discontinuation of a product at a time when it may be especially important to continue use. The Task Group recommends that a more appropriate warning be incorporated into the warning section of Drug Facts in order to provide more useful information to consumers.

4.2.1 FDA's Longstanding Policy on Warnings

A comprehensive review of FDA's OTC drug warning policy has been published.¹⁴ FDA has repeatedly stated that warnings should only contain essential information necessary to assure the proper and safe use of the OTC drug product by the

¹³ 68 Fed. Reg. at 32286

¹⁴ Soller, R.W.: When to Warn. *Regulatory Affairs Focus* 2(10): 18-21, 1997. (See [Appendix II](#)).

consumer.¹⁵ Thus, FDA does not support warnings for every possible and/or theoretical hazard that might be encountered during OTC drug use. Instead, in accordance with longstanding policy, FDA requires that OTC drug warnings be "scientifically documented, clinically significant, and important to the safe and effective use of the product by the consumer."¹⁶

FDA's long established OTC drug warning policy provides a rational and reasonable framework for decision-making by FDA to ensure that only essential information about potential risks are included in the warning label. This warning policy avoids the undesirable result of a proliferation of label statements about unsubstantiated or unlikely risks. Such a proliferation could lead to consumer confusion and to consumer desensitization to important label statements because of information overload.

4.2.2 Application of FDA's Longstanding Policy on Warnings to the Plaque Subcommittee's Proposed Warning

When using an antigingivitis/antiplaque drug product, the current language tells consumers to "stop use and consult a dentist" if their condition persists or they have symptoms of periodontitis. While consumers with these conditions should seek professional advice, placement under the "stop use" warning is not appropriate because it is inconsistent with FDA's longstanding warning policy, is inconsistent with other products in this same category, and may, in fact, be contrary to the needs of the consumer's condition.

¹⁵ 48 Fed. Reg. at 6830; 53 Fed. Reg. at 2455; 57 Fed. Reg. at 58369; 59 Fed. Reg. at 43386,43399.

¹⁶ 53 Fed. Reg. at 46204-260 and 47 Fed. Reg. at 54754.

Warnings included under the heading of "stop use and ask a dentist" are intended only for those situations in which there are signs of toxicity or other reactions that would necessitate the immediate discontinuation of product use. The warning section should contain only essential information that meets the following criteria:

- **Scientific documentation based on adequately designed and conducted studies analyzed in a scientifically acceptable manner.**

The proposed warning language has not been shown to be necessary through scientific documentation. There is no evidence to suggest that continued use of antigingivitis/antiplaque products will exacerbate gingivitis and/or plaque accumulation.

- **Clinical significance of the effect must be established to warrant the warning.**
 - All consumers using these products should be instructed to see their dentist regularly. The Task Group proposes that this directive be incorporated into the other information section on the product label.
 - The proposed warning is targeted at patients with only severe periodontitis. This wording could confuse patients by suggesting they do not need to see a dentist until/unless they have the symptoms of periodontitis. Thus, this warning may have the opposite effect of the intended action.

- If a consumer has a disease that does not improve with product use, it is likely that the condition, while it may not have progressed to the severe periodontitis described in the warning, will also benefit from professional intervention. The Task Group proposes that the following warning language be incorporated under a new section “Ask a dentist if: condition worsens or does not improve after regular use.”
- It has not been demonstrated that continued use of an antigingivitis/antiplaque product in a patient awaiting treatment for severe gingivitis or periodontitis exacerbates disease. Surely, these patients should not discontinue a regular oral hygiene regimen while awaiting treatment. Once a dentist is involved in care, patients still need to practice good oral hygiene. Use of the product by those awaiting treatment or being treated by a dentist should not be discouraged from continuing to use a safe and effective product in the interim.
- **The warning statement must be important to the safe and effective use of the product by consumers.**
 - The proposed warning statement is not required for safe and effective use of the antigingivitis/antiplaque product by consumers with gingivitis. The warning suggested by the Subcommittee is primarily directed towards populations with periodontitis who should not use this product as a substitute for

professional intervention. Instructing consumers to see their dentist regularly should alleviate this concern.

- The proposed warning may promote ineffective use of the product because consumers will discontinue use if the full effect of the product is not seen within two weeks. Clinical trials have demonstrated that the full effect of antigingivitis/antiplaque products usually takes longer than two weeks. The Task Group's proposed revision of the warning instructs consumers on appropriate use.
- The proposed warning is not consistent with antiplaque/antigingivitis products that are indicated solely for prevention of gingivitis. For this indication, it is presumed that consumers who do not have gingivitis are seeking to prevent the disease. Therefore, the warning is not meaningful to this target population.

4.2.3 Summary of Proposed Revisions to Warning Language

4.2.3.1 For All Antigingivitis and Antigingivitis/Antiplaque Products That "Control" or "Reduce"

To address these concerns, the Task Group recommends inclusion of revised language under the warnings section that incorporates consultation with a dentist if the condition does not improve and the addition of the phrase "See your dentist regularly,"

under the other information section of Drug Facts. An example of a label appears below, with recommended language underlined.

<p><i>Warnings</i></p> <p><u>Ask a dentist if</u></p> <ul style="list-style-type: none">• <u>condition worsens or does not improve after regular use</u> <p>Keep out of reach of children under 6 years of age. If more than used for (“brushing” or “rinsing”) is accidentally swallowed, get medical help or contact a Poison Control Center right away.</p>
<p><i>Directions</i></p> <ul style="list-style-type: none">• adults and children 12 years of age and older: vigorously swish 20 milliliters of rinse between your teeth twice a day for 30 seconds and then spit out. Do not swallow the rinse.• children 6 years to under 12 years of age: supervise use• children under 6 years of age: do not use
<p><i>Other Information</i></p> <ul style="list-style-type: none">• This rinse is not intended to replace brushing or flossing• <u>See your dentist regularly</u>

4.2.3.2 For All Antigingivitis and Antigingivitis/Antiplaque Products That “Prevent”

For antiplaque/antigingivitis products indicated only for prevention, the warning statement about consultation with a dentist if the condition does not improve is not necessary. Clearly, for a prevention only product, the condition in question does not exist. Nevertheless, in this case as well, the Task Group recommends inclusion of the phrase “See your dentist regularly” under the other information section of the Drug Facts box.

<p><i>Other Information</i></p> <ul style="list-style-type: none">• This rinse is not intended to replace brushing or flossing.• <u>See your dentist regularly.</u>

4.3 FDA Should Provide Alternative Labeling Options for Antigingivitis/Antiplaque Drug Products

The Task Group encourages the agency to propose alternative labeling requirements for OTC antigingivitis/antiplaque drug products (especially combination products) to comply with the requirements of the OTC drug labeling regulation.

Currently marketed Category I antigingivitis/antiplaque OTC drug products have a long and safe history of appropriate use by consumers. These products are used on a daily basis as they provide important therapeutic and often cosmetic benefits to the consumer. Antigingivitis/antiplaque products are part of a daily routine of good oral hygiene and may be marketed in small packages to permit easy use by today's highly mobile population. As the Agency has indicated that it will "consider appropriate exemptions in their respective monographs and drug marketing applications to the extent possible,"¹⁷ the Task Group recommends the agency provide reduced labeling in order to comply with the requirements of the OTC drug labeling regulation for these products. The Task Group also recommends that the Agency include these products in its definition of "convenience size"¹⁸ and to work with industry to develop reduced labeling for these products.

¹⁷ 64 Fed. Reg. at 13270

¹⁸ Comments of CTFA and CHPA, July 3, 2002 to Docket Nos. 98N-0337, 96N-0420, 95N-0259 and 90P-0201

5 Points To Consider For Testing Of OTC Antigingivitis/Antiplaque Products

Task Group Position and Recommendation

The Advance Notice of Proposed Rulemaking seeks input on final formulation testing of OTC antiplaque/antigingivitis products containing Category I active ingredients in dosage forms reviewed by the Subcommittee.

In addition, the Task Group recommends that the Agency establish appropriate test protocol designs and success criteria for two additional scenarios:

- Demonstration of clinical effectiveness of a Category I active ingredient formulated in a dosage form other than the reviewed dosage form
- Demonstration of clinical effectiveness of a Category III active ingredient to support reclassification to Category I status

For final formulation testing, the Agency should consider a guidance document approach to implement performance tests, whereas for the two additional scenarios, the Agency should consider a framework in which to evaluate the results of a gingivitis clinical trial. The guidance approach allows the Agency to take account of scientific advances and different testing methods on a current basis, instead of resorting to the resource-intensive and cumbersome notice-and-comment rulemaking approach for new methods.

A similar approach has also been used in the final monograph for antiperspirant drug products to account for minor variations in formulation. Section 350.60 (21 CFR 350.60) states:

“ An antiperspirant in finished dosage form may vary in degree of effectiveness because of minor variations in formulation. To assure the effectiveness of an antiperspirant, the Food and Drug Administration is providing guidelines that manufacturers may use in testing for effectiveness.”

The guidelines further state,:

“[t]hese guidelines do not preclude the use of alternate methods that provide scientifically valid results, subject to FDA approval.”¹⁹

The Task Group believes a similar key element-based, guideline approach for antiplaque/antigingivitis products is justified in order to take into account future scientific advancements in this area.

5.1 Final Formulation Testing

5.1.1 The Agency Should Consider a Guidance Document Approach to Implement Specifications for Final Formulation Performance Tests.

In the creation of OTC Drug Review monographs, various FDA advisory panels have considered the need for standards for final formulation testing of Category I active ingredients. The purpose was to ensure that, once an active ingredient had been shown to be safe and effective for OTC drug use, it could be used by any manufacturer meeting FDA's requirements for current good manufacturing practices. The basic principles used by FDA advisory panels to ensure that OTC drug products marketed pursuant to the OTC Drug Review final monographs are substantially equivalent to each other based on a case-by-case determination of concentration, and biological availability and/or activity.

¹⁹ 68 Fed. Reg. at 34273

The proposal identifies the need for testing requirements to establish the effectiveness of final product formulations for antiplaque/antigingivitis OTC drug products. In addition the Agency requested “specific information from interested parties on testing protocols, effectiveness criteria, and statistical methods employed to analyze the data from these tests.”

Rather than developing very detailed and specific protocols in a regulation, the Agency should issue a guidance document specifying the conditions that performance tests must meet in order to be recognized as acceptable for establishing the effectiveness of final formulations. This guidance document would provide the key elements of the protocol for each of the required final formulation tests and also list those variable elements that may be subject to change as science advances. For example, these variable elements may include specific instrumentation, reagents, or strains of bacteria. The goal is to develop a framework that is specific enough to provide confidence that Category I active ingredient formulations are both safe and effective and to allow sufficient flexibility in the testing protocols to keep up with scientific advancements.

The Task Group expects that individual companies, who have the best knowledge of testing protocols for their products, will submit detailed protocols and identify the key elements of such protocols.

5.1.2 Considerations for New or Additional Test Methods for Final Formulation Testing

The overall purpose of the final formulation testing is to determine the performance of a final product formulation compared to a clinically tested standard. The test results should provide a reasonable expectation that the previously untested

formulation will have clinical effectiveness comparable to that of the clinically tested standard.

It is likely that new or additional testing methods exist or will be developed for final formulation testing of Category I active ingredients in the reviewed dosage form. While it is difficult to provide comments on testing methods that have not been developed or presented in the proposal, the Task Group strongly supports the position that any new or additional testing methods must be representative of and consistent with human clinical endpoints related to plaque and/or gingivitis. In addition, these new or additional test methods should be shown to be valid and robust. Based upon the test methods recommended by the Subcommittee, these methods could include both short term in vivo protocols with clinical outcomes and in vitro protocols with non-clinical endpoints.

The Task Group recommends that the Agency accept and review data for new methods during the monograph process. After the monograph is finalized, new methods can be submitted as a citizen petition.

The Task Group also recommends that the Agency should allow one 6-month, single-site, randomized, negative-controlled clinical trial to be used as an alternative performance test in order to demonstrate antiplaque/antigingivitis effectiveness and that acceptance criteria be established for the evaluation of such trials.

5.1.3 Statistical Design and Success Criteria for Final Formulation Testing Involving Clinical Outcomes

When comparing a formulation to a reference standard, a short-term clinical performance test must employ methods of statistical design and analysis sufficient to

assure that the experiment is valid (e.g., the reference standard is statistically superior to the negative control) *and* that the test product is both statistically significantly superior to the negative control and statistically noninferior to the reference standard.

A general approach to addressing the noninferiority issue is to demonstrate that a test formulation mean is within a pre-specified range, referred to as the noninferiority margin, from the reference formulation mean. This approach is described in ICH E9, Statistical Principles for Clinical Trials (Section III.C.2).²⁰

For short-term clinical noninferiority testing this can be accomplished in one of two ways. The first sets a meaningful noninferiority margin by directly incorporating the reference and negative control means in the test, using as precedent the Noninferiority Fluoride Test (NIFT) included in the recent CHPA/CTFA Anticaries Task Group response to the FDA call for data. This approach has three requirements in a single study that includes a test product, a reference product (positive control), and a negative control. Each of these requirements can be assessed using an appropriate analysis of variance or analysis of covariance model. Since all of the following criteria must be simultaneously met, no multiple comparison adjustments are required.

1. The reference product mean must be statistically significantly superior to the negative control (two-sided 5% type I error rate)
2. The test product must be statistically significantly superior to the negative control (two-sided 5% type I error rate)

²⁰ 63 Fed. Reg. at 49583

3. The test product must be demonstrated to be statistically significantly superior to the average of the negative control and the reference product (one-sided 5% type I error rate)

Requirements 1 and 2 are assessed via direct contrasts of the reference and test product means with the negative control mean. Requirement 3 can be assessed by calculating a 95% one-sided confidence interval for the following contrast of means (μ s) in a statistical model and comparing that bound to 0. Noninferiority is concluded if the appropriate bound is superior to 0.

$$\mu_{\text{Test}} - 1/2(\mu_{\text{Neg}} + \mu_{\text{Reference}})$$

Requirement 1 ensures that the reference product is demonstrated to be superior to the negative control in the study. This helps ensure the validity of the study. Requirement 2 ensures that the test product is superior to negative control. Requirement 3 ensures that the test product is substantially more similar to the reference product than to the negative control.

Alternatively, in cases where the controls remain relatively consistent across studies, requirement 3 may be replaced by setting the margin to an absolute or percentage difference as compared with the reference mean. If this approach is used, the margin should be reasonable as compared to differences typically observed in previous studies comparing the reference and negative controls. As an example, if the noninferiority criterion were such that the test product mean must be less than 130% of

the reference mean, then appropriate statistical methodology would be used to test, at the one-sided 5% Type I error rate:

$$H_0: \mu_{\text{Test}} - 1.3 \mu_{\text{Ref}} \geq 0$$

Vs.

$$H_1: \mu_{\text{Test}} - 1.3 \mu_{\text{Ref}} < 0$$

Noninferiority would be concluded if H_0 is rejected.

For this alternative approach, it is expected that individual companies submitting test methods will specify the appropriate margin and provide a rationale.

5.1.4 Statistical Design and Success Criteria for Final Formulation Testing

Involving Nonclinical Outcomes

For some nonclinical tests that have quantitative endpoints, the non-inferiority approach described above may not be appropriate. Rather, the ability of the test product to meet a pre-specified quantitative criterion and a demonstration of experiment validity using positive and negative controls may be more suitable success criteria. It is expected that individual companies submitting test methods will specify appropriate success criteria and provide a rationale for their proposal.

5.1.5 Reference Products for Final Formulation Testing

Whatever test procedure is used, in order for a final formulation to be accepted as effective, it must be compared to a positive control. It is therefore important that supplies of well characterized positive control products, equivalent to the clinically tested products used to secure Category I status, be made generally available. The Task Group

recommends that the manufacturers of these products work with the U.S. Pharmacopoeia to establish and make available antigingivitis/antiplaque reference products for use as positive controls.

5.2 Testing Requirements for Category I Active Ingredients Formulated in a Dosage Form Other Than The Reviewed Dosage

For demonstration of the effectiveness of Category I active ingredients that are formulated in a dosage form other than those reviewed by the Subcommittee, the Task Group recommends that one 6-month, single-site, randomized, negative-controlled clinical trial is necessary to establish antigingivitis or antiplaque/antigingivitis effectiveness. This position is consistent with the recommendations of the Subcommittee.²¹

Individual companies may comment on specific criteria for determining clinical relevance.

5.3 Effectiveness Testing Requirements for Reclassification of a Category III Active Ingredient to Category I

For demonstration of effectiveness for the reclassification of a Category III active ingredient to Category I, the Task Group recommends that no more than two, 6-month, single-site, randomized, negative-controlled clinical studies be required to establish antigingivitis or antiplaque/antigingivitis effectiveness.

²¹68 Fed. Reg. at 32240

Individual companies may comment on specific criteria for determining clinical relevance.

6 Alcohol as an Excipient Has Not Been Shown To Be Related to Oral Cancer

6.1 *There Is No Need to Require Further Studies on Relationship between Alcohol-Containing Mouthwash Products and Oral Cancer.*

The data do not support a causal relationship between the use of alcohol-containing mouthwash products and oral cancer. In its deliberations on the association between alcohol-containing mouthwash products and oral cancer, the Subcommittee concluded:

“[T]he available data do not support a causal relationship between the use of alcohol-containing mouthrinses and oral cancer.²²”

This conclusion was reached after a thorough review of the available data (published and unpublished) and several meetings with experts, including a workshop dedicated to this topic.

The Subcommittee also acknowledged that research on oropharyngeal cancer will likely continue, and that the conclusion reached by the Subcommittee was based on the data available at the time of its deliberations. Because some studies reported a potential relationship between the use of alcohol-containing mouthrinses and oropharyngeal cancer, the Subcommittee indicated that further studies should be conducted to

²² 68 Fed Reg at 32243

investigate the relationship between high alcohol-content mouthrinses and oral/pharyngeal cancers. In fact, such studies have been published in the interim and support the Subcommittee's conclusion that there is a lack of a causal relationship between alcohol-containing mouthwash products and oral cancer.

6.1.1 Epidemiological Studies Published after the Subcommittee's Deliberations Fail to Show an Association between Alcohol-Containing Mouthwash Products and Oral Cancer

Subsequent to the Subcommittee's considerations of the association between oropharyngeal cancer and alcohol-containing mouthrinse products, additional epidemiologic studies were published. No relationship between the use of alcohol-containing mouthrinses and oropharyngeal cancer was noted in these studies.

The first study²³ was conducted by investigators from the National Institute of Dental and Craniofacial Research (NIDCR) and the National Cancer Institute (NCI). This was a large, well-designed, population-based, case-controlled epidemiologic study of oropharyngeal cancer cases in Puerto Rico between December 1992 and February 1995. This study compared 342 cases with 521 controls. The authors found no association between alcohol-containing mouthrinses and oral cancer, even in those individuals who used so-called high alcohol content products.

²³ Winn, D., Diehl, S., Brown, L., et.al. Mouthwash in the etiology of oral cancer in Puerto Rico. *Cancer Causes Control* 12:419-429, 2001. (See [Appendix II](#))

The second study²⁴ was a case-controlled study of oral epithelial dysplasia, a condition considered to be a precursor of squamous cell carcinoma. One hundred twenty-seven cases were identified from two large oral pathology laboratories. These cases were matched with 127 controls for age, gender, and referral source to the pathology laboratory. Eight variables describing mouthwash use and alcohol content were examined. Overall findings were negative for all eight variables and failed to show an association between alcohol-containing mouthrinses and oral epithelial dysplasia.

These studies add significantly to the epidemiologic literature and further support the Subcommittee's conclusion that the data do not support a causal relationship between the use of alcohol-containing mouthwash products and oral cancer.²⁵

6.1.2 Reanalysis of the NCI Study by Cole et al. Does Not Support a Causal Relationship between Alcohol-Containing Mouthwash Products and Oral Cancer

A "specificity analysis" of the data from the 1991 NCI study was conducted by Cole et al.²⁶ This analysis repeated the original study's major analysis for all cases and looked individually at cases classified as either mucosal or non-mucosal in origin (the latter including adenocarcinomas, adenoid cystic carcinoma, mucoepidermoid carcinoma, sarcoma, and Hodgkin's and other lymphomas). Since the non-mucosal lesions were

²⁴ Morse, D., Katz, R., Pendrys, D., et. al. Mouthrinse use and dentures in relation to oral epithelial dysplasia. *Oral Oncology*, 33:338-343, 1997. (See [Appendix II](#))

²⁵ 68 Fed. Reg. at 32243

²⁶ Cole, P., Rodu, B., and Mathisen, A. Alcohol-containing mouthwash and oropharyngeal cancer. A review of the epidemiology. *JADA*, 134:1079-1087, 2003. (See [Appendix II](#))

unlikely to be associated with the topical effect of mouthrinse use, it was hypothesized that if true mucosal squamous cell carcinoma were associated with mouthrinse use, the removal of the non-mucosal lesions from the analysis would result in increased odds ratios for the mucosal lesions. In fact, results of the specificity analysis, while confirming a strong association between smoking and alcohol beverage ingestion and oral cancer, failed to support an association between mouthwash use and oral cancer. The authors concluded that:

“The results of the specificity analysis preclude using this study [NCI study] to support a causal relationship between alcohol-containing mouthwash and oropharyngeal cancer.”²⁷

These analyses, taken together with the Subcommittee findings and all of the available information, do not support an association between alcohol containing mouthwash and oral cancer. Any of the weak associations found in the above studies are likely due to under-reporting or uncontrolled variables in the study.²⁸ Smoking and excessive ingestion of alcohol-containing beverages have been clearly shown to be associated with the occurrence of oral mucosal carcinoma. Studies conducted in individuals who smoke or ingest alcohol pose a significant problem of under-reporting that cannot be overlooked when interpreting the data because of its confounding effect. Given this information and the expertise that has gone into the consideration of this issue, the current state of the science leads to the conclusion that there is not a causal

²⁷ Cole. *supra*, at 1087. (See [Appendix II](#))

²⁸ Shapiro S et al. Alcohol-containing mouthwashes and oropharyngeal cancer. A spurious association due to under ascertainment of confounders. *Am J Epidemiol*, 144: 1091-1095, 1996. (See [Appendix II](#))

relationship between alcohol-containing mouthrinses and oral cancer and, therefore, that further study is not warranted.

6.2 Alcohol-Containing Mouthrinse Products Do Not Affect the Permeability of the Oral Mucosa under Conditions of Normal Product Use

Critical analyses of published studies showing that alcohol enhances the penetration of carcinogens through the oral mucosa do not support such an enhancement of permeability under conditions of actual mouthrinse use.

The Subcommittee indicated that further research should be done “to investigate the role of alcohol as an enhancer of the penetration of carcinogens through the oral mucosa.”²⁹ This recommendation is based largely on a study by Squier et al.³⁰ that showed that, in the presence of nicotine, ethanol enhanced the penetration of nitrosonornicotine across the oral mucosa. This in vitro study utilized porcine mucosa and exposure periods of one hour and greater. The authors note that the findings of this study can only be extrapolated to the in vivo situation “with caution” since factors such as salivary flow and the salivary mucin coating can modify the permeability of the mucosal surface.

²⁹ 68 Fed. Reg. at 32242

³⁰ Squier, CA., Cox, P., and Hall, BK. Enhanced penetration of nitrosonornicotine across the oral mucosa in the presence of ethanol. *J Oral Path.* 15:276-279, 1986. (See [Appendix II](#))

Subsequent to the Subcommittee's workshop, a study was conducted³¹ specifically to assess the effect of Listerine® mouthrinse on oral permeability using an in vitro model similar to that used in the experiments of Squier et al. This study, however, used exposure times more consistent with actual clinical use of mouthwash. These exposure times included 30 seconds as well as longer exposure times of 2 and 15 minutes. The investigators also examined the surface morphology of the tissue using scanning electron microscopy. As compared to a positive and negative control, mouthwash pretreatment of either buccal mucosa or ventral tongue had no effect on the permeability or surface typography of these tissues.

These study results support the safety of alcohol-containing mouthrinses and suggest that in considering experimental models to investigate mucosal permeability, it is critical to determine the applicability of the model being used to the specific question being investigated.

6.3 Testing of Individual Mouthrinse Components for Potential Cancer Risk Is Not Necessary

Testing of individual mouthwash components for carcinogenic potential is not necessary given the lack of an association between alcohol-containing mouthwash and oral cancer.

The Subcommittee suggested further studies on the possible cancer risk associated with high alcohol-content mouthrinses should be conducted and that these studies should

³¹ Bhageerutty, Y, Cruchley, AT., and Williams, DM. Effect of an alcohol containing mouthwash on mucosal permeability. J. Dent. Res 77:abstr. 1091, 1998. (See [Appendix II](#))

include testing various components of the mouthrinse and pertinent dietary ingredients.³²

As noted above, additional epidemiologic studies have been conducted and have led to the conclusion that there is no association between alcohol-containing mouthwash and oral cancer. Accordingly, there is no apparent scientific rationale for the testing of individual mouthrinse components for oral cancer because the evidence indicates that the mouthrinse formulations as a whole are not associated with oral cancer. It is not apparent what is meant by “pertinent dietary ingredients” and the rationale for testing such ingredients. Unlike alcoholic beverage consumption, where the alcoholic beverage is oftentimes consumed at the time of eating, rinsing with mouthrinse products does not occur at the time of eating. Considerations for testing the components of mouthrinse product for their cancer potential is therefore not necessary as safety of mouthrinse product has already been established and the testing of mouthrinse products with “pertinent dietary ingredients” is not applicable to the product’s use.

7 Mechanisms Other than Plaque Mass Reduction that Produce an Antigingivitis Effect

The agency has requested comment on “whether products that are solely antigingivitis agents, i.e., products that do not significantly reduce plaque, constitute appropriate OTC drug products.”³³ The Subcommittee stated “that ingredients that work primarily by means other than plaque reduction would be inappropriate for use in OTC

³² 68 Fed. Reg. at 32241

³³ 68 Fed. Reg. at 32232

antigingivitis drug products because these products may mask the symptoms of a more serious condition and cause consumers to delay seeking the advice of a dentist.”³⁴

The Task Group believes these types of agents can be divided into two groups. The first group of agents are those that reduce gingivitis but do not demonstrate a clinically measurable plaque mass reduction but still achieve their gingivitis reduction through a plaque-mediated mechanism such as reduction of specific bacterial pathogens which could significantly reduce the plaque virulence but would not necessarily produce a measurable reduction in the overall plaque mass. Other agents may reduce plaque metabolism, providing a “bacterio-static effect” as opposed to a plaque mass reduction. Therefore, agents that achieve gingivitis reduction via a plaque mediated mechanism, other than plaque mass reduction, should clearly be considered as safe and effective OTC antigingivitis drugs and should be awarded indications/claims commensurate with their antiplaque effects.

The second group of agents are those that achieve their gingivitis benefit by a non-plaque mediated mechanism. The Task Group’s position is that this should be assessed on a case-by-case, weight of the evidence basis since it is likely that such a product would present little risk of masking the signs/symptoms of a more serious condition. An antigingivitis-only product that works through a non-plaque mediated mechanism(s) *may*, in some cases, be appropriate for OTC use. Certainly, any such product would require review by the Agency to determine its safety and effectiveness.

³⁴ Ibid

All of the Category I or III active ingredients of this rulemaking are associated with achieving gingivitis reductions via a plaque mediated mechanism. For other agents that fall into the second category of achieving gingivitis reductions via a non-plaque mediated mechanism, these agents would require approval by a new drug application. The Task Group recommends that FDA keep an open mind and determine the OTC drug status based on the data.

8 The Monograph Should Permit Any Dosage Form Suitable for Topical Oral Administration

As published in the Federal Register, the proposed monograph would limit antiplaque/antigingivitis dosage forms to mouthwash products for two of the three Category I ingredients (cetylpyridinium chloride and a fixed combination of essential oils (eucalyptol, menthol, methyl salicylate and thymol)) and to toothpaste products for the third Category I ingredient (stannous fluoride). This does not conform to the conclusions and recommendations of the Subcommittee as expressed during their meetings and in their report.

The report of the Subcommittee states

“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.”³⁵

³⁵ 68 Fed. Reg. at 32240

Yet the proposed monograph itself does not permit all of the “traditional dosage forms” for each of the Category I active ingredients specifically recommended by the panel. The panel specifically considered “traditional” dosage forms such as dentifrice, gels, paste and rinse products³⁶. In addition, the panel recommended that for additional dosage forms, a six-month trial is recommended.

The Task Group recommends that FDA adopt the recommendations of the Subcommittee and incorporate language in the monograph that would permit any dosage form that is suitable for topical oral administration, conditioned upon successful completion of one, six-month clinical trial.

During the Subcommittee meeting on May 27, 1998, Warner-Lambert representatives made two presentations pertinent to the issue of dosage forms. The first presentation summarized the information set forth in a memorandum dated May 13, 1998, that documented the flexible approach to dosage forms that has uniformly been followed throughout the OTC Drug Review proceedings.³⁷ It sets forth numerous examples where proposed, tentative final, and final monographs have permitted “a form suitable for oral administration” or “a form suitable for topical administration.” The second presentation pointed out that, with a broader array of appropriate dosage forms for oral topical administration, it would be necessary to incorporate a mandatory performance test procedure in order to assure the effectiveness of the final formulation, as

³⁶ 68 Fed. Reg. at 32240

³⁷ Memorandum from Warner-Lambert Company to FDA(1998) (See [Appendix III](#))

has been done in other monographs. The second presentation recommended a single six-month clinical trial to serve that purpose, with which the Subcommittee agreed.

On the basis of these two presentations the Subcommittee concluded, without dissent, that flexibility in dosage forms should be adopted. The Subcommittee mentioned a number of different possible dosage forms, including toothpaste, tray delivery gels, chewing gum, dental floss, and others. At this point, Dr. Linda Katz of FDA stated that the Subcommittee was expanding the permitted dosage forms too far, and requested that they be limited to traditional dosage forms. The Subcommittee accepted this FDA limitation without discussion. Dr. Katz agreed that toothpaste and tray delivery gels, as well as mouthwash products, are traditional dosage forms for these kinds of products.

The following day there was no discussion of this matter because the entire day was devoted to appropriate labeling. On the next day, May 29, 1998, there was discussion throughout the day about appropriate dosage forms for antiplaque/antigingivitis products and about the type of final dosage form performance testing that would be appropriate for new types of dosage forms. When FDA representatives again referred to traditional dosage forms, it was pointed out that this terminology has never previously been used in an OTC drug monograph and that there is no list of so-called traditional dosage forms. Dr. Katz agreed. The Subcommittee thereafter did not refer to traditional dosage forms, and its unanimous decision, as stated by Chairman Genco³⁸, was:

³⁸ Nonprescription Drugs Advisory Committee, Dental Plaque Subcommittee, Proceedings, p. 110 (1998).

“that the monograph cover dentifrice, mouth rinse, gels and other non-ingestible forms meant to be expectorated of agents, anti-plaque and anti-gingivitis agents.

But that these new dosage forms be subjected to six-month clinical trial in which efficacy and safety is assessed.”

A six-month clinical trial was agreed upon as applicable to a new dosage form because there would be no data reviewed by the Subcommittee for these active ingredients in the new dosage form.

The Subcommittee meeting on October 22, 1998, began with a request by an academic scientist to add chewing gum as an acceptable dosage form. Because chewing gum ingredients are ingested rather than expectorated, however, it was rejected. The Subcommittee reiterated its decision to require one six-month clinical trial for each new dosage form beyond those specifically reviewed by the Subcommittee. There was no mention of limiting acceptable dosage forms to traditional forms.

At the first day of the final meeting of the Subcommittee, on December 2, 1998, Chairman Genco reiterated the decision of the Subcommittee³⁹:

“So to clarify, Agent X in the monograph is Category I. Category I for safety and efficacy is in today a mouth rinse. Somebody wants to put it into a dentifrice, a toothpaste, then the six month trial applies. If they make another formulation of Agent X in a mouth rinse, then a six-month trial is not needed, but bioequivalence, based upon in vivo, ex vivo experiments are needed.”

Again, the Subcommittee did not limit its recommendation to traditional dosage forms.

Thus, from the initial discussion of this matter on May 27, 1998, to the final discussion on December 2, 1998, the Subcommittee did not change its basic determination that the antiplaque/antigingivitis monograph should permit any appropriate

³⁹ Nonprescription Drugs Advisory Committee, Dental Plaque Subcommittee, Proceedings, p. 85 (1998).

oral topical dosage form. The Subcommittee repeatedly rejected limiting the monograph to the dosage forms specifically presented to the Subcommittee, or to traditional dosage forms as urged by FDA, and instead decided to encompass this broader category.

The proposed monograph published in the Federal Register does not reflect these Subcommittee decisions. Contrary to what the Subcommittee concluded, the proposed monograph as published is limited to mouthwash products for two active ingredients and toothpaste for one. It is inconsistent both with the Subcommittee deliberations and with the substantial precedents set forth in the memorandum submitted to the Subcommittee dated May 13, 1998 ([Appendix III](#)).

Preambles to prior FDA proposed, tentative final, and final monographs recognize that flexibility is a desirable goal in determining suitable conditions for use of OTC drug products, as long as safety and effectiveness can be assured. For example, one panel has stated that it:

“did not intend to restrict ingenuity in product design as long as the product accomplishes the claimed effect and met the same formulation requirements of safety and effectiveness as any other dosage form”⁴⁰

This is what the Subcommittee that reviewed antiplaque/antigingivitis products intended, and that intent should have been recognized in the proposed monograph and should now be incorporated in the tentative final and final monographs.

The Task Group recognizes, as did the May 13, 1998 memorandum ([Appendix III](#)), that allowing flexibility in dosage forms requires that every formulation satisfy a performance test of effectiveness. That performance test is in fact included in the preamble to the proposed monograph as quoted above -- a single six-month clinical trial.

It is this performance test that will assure the effectiveness of whatever dosage form is chosen for a particular antiplaque/antigingivitis product.

Under the OTC Drug Review, FDA and its OTC advisory panels have taken a flexible approach to dosage forms. Most OTC drug monographs do not specify a particular dosage form. Of direct relevance to antigingivitis/antiplaque oral care drug products are the many other proposed, tentative final, and final monographs documented in the May 13, 1998 memorandum ([Appendix III](#)) which permit categories of drug products “in a form suitable for topical administration.” Examples include those for antifungal, external analgesic, topical otic, antiperspirant drug products, and skin protectants. In the absence of any justification for limiting the dosage forms, the Task Group recommends that FDA make the antigingivitis/antiplaque monograph consistent with the other topical drug monographs that have provided flexibility for dosage forms.

The Task Group therefore recommends that FDA follow the recommendations of the Subcommittee and expand the permitted dosage forms to include any dosage form suitable for oral topical administration. This, coupled with the requirement for one six month trial as a performance test, will assure flexibility in developing new antiplaque/antigingivitis products that meet unambiguous standards for effectiveness.

⁴⁰ 53 Fed. Reg. at 30756, 30762

We ask that the Agency give careful consideration to these comments. If the Task Group can be of further assistance, please do not hesitate to contact the undersigned.

Respectfully submitted on behalf of the CHPA/CTFA Joint Oral Care Task Group,

Douglas Ws. Bierer, Ph.D.
Vice President - Regulatory & Scientific Affairs
Consumer Healthcare Products Association

[Appendix I – Regulatory Analysis of the Cosmetic/Drug Status of Antiplatelet Claims](#)
[Appendix II - References](#)
[Appendix III – May 1998 Letter from Warner-Lambert Company to Robert Sherman, FDA](#)

cc: E. H. Anderson, CTFA
Charles J. Ganley (HFD-560)
Robert L. Sherman (HFD-560)

DB/mm