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

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

On May 29, 2003 the Food and Drug Administration published a proposed monograph for OTC antigingivitis/antiplaque drug products.

Pfizer Inc has a considerable interest in this proceeding. Pfizer manufactures and markets important consumer products that will be covered by the final monograph that emerges from this proceeding. For that reason, Pfizer and, prior to its merger with Pfizer, the Warner-Lambert Co. made substantial submissions to the administrative record and participated in the public meetings of the advisory committees that considered OTC antiplaque and antigingivitis drug products during 1993-1998.

At this time Pfizer is submitting the following comments:

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I. Oral Care Products Making Only Cosmetic-Related Plaque Claims Are Properly Regulated as Cosmetics and Not as Drugs Under the FD&C Act

The Food and Drug Administration (FDA) has long recognized that the OTC Drug Review does not extend to purely cosmetic products and labeling claims. Oral care products which are intended for the removal or reduction of dental plaque have long been marketed to and used by consumers for purely cosmetic purposes such as cleaning the teeth, improving appearance, combating malodor, and making the mouth feel fresh and clean. In the absence of claims that they are intended to affect the structure or function of the body, or prevent or treat dental or gum disease, such products may only be regulated as cosmetics under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The Over-the-Counter Plaque Products Subcommittee (the Subcommittee) departed from the clear provisions of the FD&C Act when it recommended that all claims regarding plaque reduction be classified as drug claims, even when those claims are explicitly limited to unambiguous and unequivocal cosmetic benefits. The Subcommittee's position would subject all products whose labeling refers to "plaque" to regulation as drugs on the theory that use of that term may be misleading and may be interpreted by consumers as drug claims. Pfizer urges FDA to reject the Subcommittee's

speculation and to recognize that a product with properly qualified cosmetic claims related to plaque is solely a cosmetic and not a drug.

As discussed below, in order to be classified as a drug under the FD&C Act, a product must be "intended" to affect the structure or a function of the body, or to prevent or treat disease. It is well settled that the "intended use" of a product is determined with reference to the totality of advertising and labeling claims being made for that product. As these comments will show, the Subcommittee's views are inconsistent with the FD&C Act, FDA regulations, and judicial and agency precedent. These comments describe the relevant history of the "intended use" doctrine and, based on application of that doctrine, conclude that products making only cosmetic-related plaque claims remain subject to regulation solely as cosmetics.

DISCUSSION

A. Congress Intended To Distinguish Drugs From Cosmetics On The Basis Of The Claims Made For These Products

The FD&C Act defines a "drug" as any article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention, of disease," or any article "intended to affect the structure or any function of the body" FD&C Act § 201(g)(1)(B)&(C). A "cosmetic" is an article "intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance." FD&C Act § 201(i)(1).

The Subcommittee correctly observes that "[s]ome products may not clearly fall under one definition or the other," 68 Fed. Reg. at 32238, and the statute makes clear that

the terms are not mutually exclusive. FD&C Act § 509. As is evident from the cosmetic definition itself, however, Congress contemplated that even articles which are "introduced into" the body, and which presumably work by having some incidental effect on the structure or function of the body, may be properly categorized as cosmetics. Indeed, the definition was intentionally "drawn in broad terms to include all substances and preparations, other than ordinary toilet or household soap, intended for cleansing, or altering the appearance of, or promoting the attractiveness of the person," whether "used externally, orificially, or even internally as in the case of the use of arsenic for clearing the complexion." S. Rep. No. 361, 74th Cong., 1st Sess. 3 (1935).

The structure-or-function definition of drug was not intended to reach traditional cosmetic products. The rationale for adding this definition to those already appearing in the predecessor 1906 Act was explained as follows:

> There are products on the market now that escape control either under the definition of "food" or under the definition of "drugs" in the present act, such as slenderizing products, reducing products. Obesity is not itself a disease in all instances and products advocated and sold for the treatment of obesity, as a matter of fact, are not always subject to the terms of this act.

"Foods, Drugs, and Cosmetics": Hearings on S. 2800 Before the Senate Committee on Commerce, 73d Cong., 2d Sess. 516 (1934) (statement of W.G. Campbell, Chief of FDA). A number of courts interpreting the structure-or-function definition of the term "drug" have underscored this narrow congressional purpose. E.g., E.R. Squibb & Sons, Inc. v. Bowen, 870 F.2d 678, 682-83 (D.C. Cir. 1989) (and cases cited therein); Rodriguez, Cosmetic or Drug? The Minotaur's Labyrinth Revisited, 44 Food Drug Cosm.

L.J. 63 (1989). Ultimately, the intended uses of a product dictate whether it will be regarded as a drug or a cosmetic, or both.

As recently as 1998, the United States Court of Appeals for the Fourth Circuit observed that "no court has ever found that a product is 'intended for use' or 'intended to affect' within the meaning of the [FD&C Act] absent manufacturer claims as to that product's use." Brown & Williamson Tobacco Corp. v. FDA, 153 F.3d 155, 163 (4th Cir. 1998) (internal quotation marks omitted) (citing Coyne Beahm, Inc. v. FDA, 966 F. Supp. 1374, 1390 (M.D.N.C. 1997)), aff'd on other grounds, 529 U.S. 120 (2000); see also United States v. Undetermined Quantities . . ."Pets Smellfree," 22 F.3d 235, 240 (10th Cir. 1994) ("PSF's claims [in labeling and promotional materials] . . . bring Smellfree within the scope of § [201](g)(1)(C)."); United States v. Storage Spaces Designated Nos. "8" and "49," 777 F.2d 1363, 1367 n.6 (9th Cir. 1985) (relying on "the manner in which the products [were] promoted and advertised" in finding that the products were drugs under Section 321(g)(1)(C)); United States v. An Article of Device . . . "Amblyo-Syntonizer"), 261 F. Supp. 243, 244 (D. Neb. 1966) (articles were sold to "only those optometrists who take courses [from the distributor] concerning the purpose and use of the device").

This focus on intended uses rather than actual effects has been confirmed in other judicial decisions. For instance, in National Nutritional Foods Association v. Mathews, 557 F.2d 325, 333-36 (2d Cir. 1977), the court held that FDA could not subject dietary supplements containing high levels of Vitamins A and D to regulation as drugs unless it could identify labeling claims or other evidence to indicate that these products were

intended to function as drugs. Similarly, in Action on Smoking & Health (ASH) v. FDA, 655 F.2d 236, 239-41 (D.C. Cir. 1980), the court held that cigarettes were not drugs simply because they affected the structure or function of the body unless there was evidence that the products were intended to be used for this purpose. By comparison, where claims of therapeutic benefits or of structure-or-function effects are made for common products, they will be regulated as drugs.[1]

The concept of "intended use" has also been applied to medical devices. In a recent comprehensive legal review of the FD&C Act and all applicable judicial precedent, FDA has reinforced the position that a manufacturer's marketing representations determine a product's "intended use." Letter dated October 17, 2002 to Jeffrey Gibbs from Daniel E. Troy, FDA Chief Counsel (October 17, 2002). Distinguishing between identical, implantable digital transponders or "chips" -- one providing access to information necessary to identify livestock, and the other facilitating access to information for use by medical professionals in treating patients -- FDA found that the intended use of each chip was the sole determining factor in deciding whether the chips were covered by the FD&C Act. Specifically, FDA concluded that:

> FDA's medical device jurisdiction ... extends only to such products that are marketed by their manufacturers or distributors with claims of effects on the structure or a function of the body. In the language of the statute itself, the product must be "intended to" affect the

[1] E.g., Nutrilab, Inc. v. Schweiker, 713 F.2d 335, 337-38 (7th Cir. 1983) (starch blocker tablets); Bradley v. United States, 264 F. 79, 81-82 (5th Cir. 1920) (water); United States v. An Article of Drug...U.S. Fancy Pure Honey, 218 F. Supp. 208, 211 (E.D. Mich. 1963), aff'd, 344 F.2d 288 (6th Cir. 1965); United States v. 46 Cartons...Fairfax Cigarettes, 113 F. Supp. 336, 337 (D.N.J. 1953).

> structure or a function of the body. It is well settled that intended use is determined with reference to marketing claims.

FDA October 17, 2002 Letter at 3. The letter stated that a foreseeable effect on the structure or function of the body is not sufficient to bring a product within the definition of a drug where the product's claims make no reference to such an effect.

B. Oral Care Product Claims Associated Only With The Cosmetic Benefits Of Plaque Reduction Are Solely Cosmetic Product Claims

The FDA regulations identifying "cosmetic product categories" recognize that "dentifrices," "mouthwashes and breath fresheners," and "other oral hygiene products" fall within the definition of a cosmetic. 21 C.F.R. § 720.4(c)(9). Indeed, an oral hygiene product has been classified since 1938 as a cosmetic if no drug claims are made for it. For example, prior to the introduction of fluoride, all toothpaste products in the United States were classified as cosmetics and not drugs because they were sold solely for the purpose of cleaning or whitening teeth and freshening breath. Even after the introduction of fluoride, non-fluoride dentifrices continue to be regulated exclusively as cosmetics in the absence of disease claims even though their ability to remove plaque and food debris may have incidental disease-prevention effects. FDA also has classified traditional mouthwashes as cosmetics for many years because they claim only to freshen breath and reduce malodor.[2] Similarly, the agency has confirmed that, although antimicrobial soaps

[2] FDA's OTC advisory panel on Oral Health Care Drugs affirmed that mouthwashes used for cleansing and deodorizing the mouth are cosmetics in the absence of drug claims. 47 Fed. Reg. 22760, 22778-79, 22843-44 (May 25, 1982).

may reduce bacteria on the skin that cause disease, "[s]oap products that contain antimicrobial ingredients will be considered 'cosmetics,' and not 'drugs,' if only deodorant claims (or other cosmetic claims) are made for the products." 56 Fed. Reg. 33644, 33648 (July 22, 1991). FDA also treats skin moisturizers labeled for cosmetic uses as cosmetics, despite the fact that they prevent skin cracking, which can lead to infection. 21 C.F.R. § 720.4(c)(12)(vi); United States v. An Article ... *"Sudden Change"*, 409 F.2d 734, 741-42 n.10. These examples confirm that a cosmetic product is not also a drug simply because it has collateral therapeutic benefits or effects on the body's structure or function.

The Subcommittee ignored the agency's long-standing legal interpretation with regard to intended use classification when it recommended that "any reference to the control of dental plaque or its equivalents, with or without qualification, should be interpreted as a drug claim." 68 Fed. Reg. at 32239. The publication of a panel report as an advance notice of proposed rulemaking does not, however, represent the position of the agency. 68 Fed. Reg. at 32232 ("This document . . . does not necessarily reflect the agency's position on any particular matter contained in it."). Indeed, in a footnote to the panel report, FDA specifically questioned the recommendation concerning the classification of antiplaque products, noting that "[t]he legal opinions of this scientific panel in this area may not and do not necessarily reflect FDA's position." 68 Fed. Reg. at 32238.

Pfizer acknowledges that an antiplaque product properly may be subject to regulation as a drug where its labeling and advertising shows that it is offered to prevent

or treat oral disease or to affect the structure or function of the oral cavity. On the other hand, the relevant statutory provisions and FDA regulations clearly dictate that if a product -- including an antiplaque product -- is intended to be used solely for cosmetic purposes, it is subject to regulation as a cosmetic, and only as a cosmetic.

C. Claims That An Oral Care Product Provides Cosmetic Plaque Reduction Benefits Are Not Claims That A Product Will Affect The Structure Or Any Function Of The Body

The previous section explained that an oral care product associated only with cosmetic plaque reduction benefits does not imply any therapeutic effect. Nor does such a claim qualify the product as a drug on the grounds that it claims to "affect the structure or any function of the body." FD&C Act § 201(g)(1)(C). Although this has been the subject of significant controversy with regard to anti-wrinkle claims for skin care products, where the agency has asserted that such claims may reflect an intent to affect the structure or function of the body, no similar difficulty is posed by oral care products making cosmetic plaque removal claims. In E.R. Squibb & Sons, the United States Court of Appeals for the District of Columbia Circuit denied a petition to review FDA's decision to withdraw approvals for several combination drugs where the manufacturer was unable to demonstrate any therapeutic significance to the claimed effectiveness of the antifungal component in suppressing candidal overgrowth in the intestinal tract that resulted from the effect of the antibiotic component of the combination. The manufacturer argued unsuccessfully that it need only demonstrate effectiveness with

regard to an intent "to affect the structure or any function of the body of man." The court concluded:

> First, it is questionable whether a drug that acts only upon non-human organisms that happen to reside within the human body can properly be understood as affecting the "body of man" (as opposed to the "prevention of disease in man") within the meaning of the definition. Second, assuming that such organisms could be understood as part of the human body, a drug that suppresses their growth does not affect the "structure" or "function" of the human body as the courts have construed those terms.

870 F.2d at 682. The court emphasized that the structure-or-function prong of the drug definition "is relatively narrow, and was not intended to encompass all articles that might have some remote physical effect upon the body." Id.

After reviewing the available case law interpreting the structure-or-function definition of the term "drug" and discussing Congress's limited intent in adding this definition, the court in Squibb concluded as follows:

> The suppression effect Squibb claims...would simply reduce the number of non-human organisms residing within the intestinal tract. Candida organisms are hardly part of the physical "structure" of the human body, nor does their suppression affect any "function" of the body in the sense that articles that induce sleep or inhibit digestion do.
>
> Mysteclin's undisputed status as a drug, therefore, appears to depend upon its being an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man...."

Id. at 683. To be sure, this case did not involve a dispute over whether a product was properly classified as a drug or as a cosmetic, but the court's opinion makes it clear that

any such dispute with regard to an antiplaque product would depend on the application of the disease-related definition of drug rather than the structure-or-function definition. Thus, the fact that cosmetic claims for the reduction of plaque are made in the labeling for oral care products cannot convert such claims into drug claims.

The principal question in all cases concerns the intended uses of a product as revealed in its labeling or advertising. Sudden Change, 409 F.2d at 739-42; United States v. An Article... "Line Away", 415 F.2d 369, 371-72 (3d Cir. 1969); 21 C.F.R. § 201.128. Without such a rule, nearly every cosmetic product could be regulated as a drug because any product that touches the skin inherently affects the structure or function of the body in some respect.

D. The Rationale for the Subcommittee's Recommendation Violates the First Amendment to the United States Constitution

The Subcommittee states that "[t]he claim that a product significantly reduces dental plaque (statistically speaking) may mislead people into thinking that the reduction is therapeutically significant" and thus that:

> people may purchase a product with the mistaken notion that a therapeutic benefit may be derived from its use, instead of seeking effective care for potential signs and symptoms of disease.

68 Fed. Reg. at 32238-39. This assertion is contradicted by an industry study that is a part of the administrative record,[3] and does not meet the relevant burden of proof for a finding by FDA that all plaque claims are drug claims. Thus the Subcommittee's statements must be understood as nothing more than the unsubstantiated personal views of individuals who, while expert on the issue of dental medicine and science, have little knowledge, experience, or expertise in the field of consumer understanding of product labeling. As such, these statements of the Subcommittee carry no weight or credibility.

Evidence of intended use must be interpreted from the viewpoint of consumers to whom product claims are directed. The proper focus is "how ... claims are understood by the buying public," and whether the claims as so understood may fairly be said to represent that the product is a drug. Sudden Change, 409 F.2d at 742. Whenever FDA seeks to exert its statutory authority to regulate a product or class of products as drugs under the FD&C Act, whether by rulemaking or case-by-case enforcement action, the burden rests with the agency to establish by objective factual evidence that the products at issue are in fact intended to be used as drugs.[4] As one federal court has stated,

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[3] Presentation of Plaque Statement Consumer Research conducted for CHPA/CTFA by Walker Research (June 1994).

[4] See, e.g., National Nutritional Foods Ass'n v. Mathews, 557 F.2d 325 (2d Cir. 1977) (dispositive issue in challenge to rulemaking is adequacy of FDA support for classifying products sought to be regulated as drugs); National Nutritional Foods Ass'n v. FDA, 504 F.2d 761 (2d Cir. 1974), cert. denied, 420 U.S. 946 (1975); United States v. 23 7/12 Dozen Bottles ... "Lee's Save the Baby", 44 F.2d 831, 833-34 (D. Conn. 1930) ("Lee's Save the Baby") (FDA bears burden in misbranding action to show that labeling contains representation alleged by FDA), United States v. Articles of Drug, Etc., 263 F Supp 212, 217 (D. Neb. 1967) ("Vit-Ra-Tox") (FDA bears burden of proving drug status in misbranding action), –General Accounting Office, Lack of Authority Hampers Attempts to Increase Cosmetic Safety, HRD-78-139 (Aug. 8, 1978) at 132 (Statement by Department of Health, Education, and Welfare) (cosmetic/drug determinations by FDA require case-by-case examination of facts to determine intended use); 48 Fed. Reg. 6820, 6822 (Feb. 15, 1983) (applying same standard to Over-The-Counter Drug Review).

determinations of drug status are not left to FDA's "unbridled discretion to act to protect the public health but must be in accordance with the statutory definitions."[5]

Given the long marketing history of oral care products making cosmetic plaque claims, consumers are not likely to misunderstand such claims as promising some therapeutic effect. It is wholly inappropriate to predicate an important agency decision on the Subcommittee's unsubstantiated conjecture that consumers are likely to purchase such products "with the mistaken notion that a therapeutic benefit may be derived from its use." 68 Fed. Reg. at 32238.

The pertinent legislative history supports this position. Specifically, the Senate Report accompanying the legislation that became the FD&C Act states:

> The use to which the product is to be put will determine the category into which it will fall. . . . The manufacturer of the article, through his representations in connection with its sale, can determine the use to which the article is to be put.

S. Rep. No. 74-361, at 4 (1935) (emphasis added); see also "Foods, Drug, and Cosmetics": Hearings on S. 2800 Before the Senate Committee on Commerce, at 517-18 (1934) (a table would be subject to FDA jurisdiction only if claimed to have medical application). As the D.C. Circuit found, that intended use is determined by manufacturer marketing claims "has now been accepted as a matter of statutory interpretation" by the federal courts. ASH, 655 F.2d at, 238-39.

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[5] National Nutritional Foods Ass'n v. Matthews, 557 F.2d at 334-35.

Based on its finding that "effective control of gingivitis [must] be accompanied by effective control of dental plaque," the Subcommittee illogically concludes that plaque reduction is inextricably tied in consumers' minds to therapeutic benefits. While the Subcommittee is correct that by preventing, removing, or reducing plaque accumulation, antiplaque products can help prevent caries and periodontal diseases, it fails to recognize that antiplaque products also have well-recognized cosmetic benefits. For example, plaque reduction leads to cleaner and whiter teeth, less formation of unsightly tartar, a cleaner-feeling mouth, smoother-feeling teeth, and fresher breath. When only these cosmetic benefits are claimed, a product is solely a cosmetic under the FD&C Act.

In the case of tartar, the Subcommittee concluded that all supragingival tartar (calculus) claims are solely cosmetic in nature. Given that plaque is a precursor of tartar, it would be wholly illogical for a claim to prevent the source (plaque) of a *cosmetic* problem (tartar) to be deemed a drug claim in the eyes of consumers.

Even if a cosmetic plaque claim were to be shown to raise a potential for reasonable consumers to be confused or to misunderstand the claim, recent judicial decisions have unambiguously held that FDA is required by the First Amendment to the United States Constitution to permit the use of qualifications or additional explanatory information, in order to assure that the claim is not misleading, rather than banning the claim.[6] These decisions allow FDA to ban a truthful and accurate claim only if the agency can show, with "empirical evidence," that no possible qualification can prevent

the claim from being misleading. As the Supreme Court informed FDA in the recent pharmacy compounding decision: "If the First Amendment means anything, it means that regulating speech must be a last – not first – resort."[7]

In summary, use of the term "plaque" does not render a product claim a drug claim. Rather, such a determination must be made by reference to the "intended use" of the product in question. Consistent with FDA regulations and First Amendment principles, and in accordance with well-established agency and judicial precedent, FDA should set aside the Subcommittee's assertions on this point, and should conclude that oral care product claims associated with the cosmetic benefits of plaque reduction are solely cosmetic product claims.

II. Both *In Vivo* and *In Vitro* Testing Should Be Required for Products Containing the Fixed Combination of Essential Oils

Proposed section § 356.92(b) states that "One of the following tests should be conducted" and then lists an *in vitro* microbiological test, and a clinical test to demonstrate *in vivo* activity. This is inconsistent with the basis of Warner-Lambert Co.'s April 27, 1998 submission, which specifically states: "A combination of *in vitro* and *in*

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[6] Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999), rehearing denied, 172 F.3d 72 (D.C. Cir. 1999) (en banc), 130 F. Supp. 2d 105 (D.D.C. 2001), 141 F.Supp. 2d 105 (D.D.C. 2001); Whitaker v. Thompson, 248 F. Supp. 2d 1 (D.D.C. 2002).

[7] Thompson v. Western States Medical Center, 535 U.S. 357, 373 (2002).

vivo tests should be required since *in vitro* tests alone, while able to confirm the antimicrobial activity of a given formulation, are not necessarily indicative of the *in vivo* antiplaque/antigingivitis activity of the formulation." This is also inconsistent with Section F of the Subcommittee report. 68 Fed. Reg. at 32240-41.

The overall purpose of the final formulation test methods is to determine the comparable effectiveness of a final product formulation and a clinically tested standard. The test results should provide a reasonable expectation that the untested new formulation will have clinical effectiveness comparable to that of the standard formulation containing the same level of Category I active ingredient. The Subcommittee recognized the need for such testing because the way a product is formulated can have a significant impact on the effectiveness of active ingredients. The *in vitro* test confirms that the antimicrobial spectrum of activity of the formulation has been retained and is required for reasons of both product effectiveness and safety with long term use. The *in vivo* test is necessary because a biofilm, such as bacterial plaque, presents a more rigorous challenge than do the planktonic organisms used for *in vitro* testing, and therefore this test will confirm that the clinical antiplaque/antigingivitis effectiveness of the formulation has been retained. Thus, the scientific rationale for requiring both types of tests is based on the concept that the two tests separately address two important product attributes, spectrum of antimicrobial activity, and *in vivo* clinical effectiveness.

For antiplaque/antigingivitis products containing the fixed combination of essential oils, it should be demonstrated that:

1. The final formulation has the same *in vitro* antimicrobial spectrum of activity as the standard **and**

2. The final formulation has a level of clinically relevant *in vivo* effectiveness noninferior to the reference standard.

Representative protocols for the two methods were included in the 1998 Warner-Lambert submission to the Subcommittee. This submission is referenced in the Subcommittee report. 68 Fed. Reg. at 32241.

III. The Monograph Should Include Professional Labeling for the Fixed Combination of Essential Oils

On August 20, 1998, Warner-Lambert forwarded a submission to the Subcommittee in support of professional labeling for Listerine Antiseptic with the indication, "For the reduction of viable aerosolized bacteria during dental procedures." The submission contained research reports and peer-reviewed publications[8,9,10] for four controlled clinical studies. These studies demonstrated that rinsing for 30 seconds with 20 ml. of Listerine Antiseptic mouthrinse prior to a representative aerosol-producing dental procedure can result in statistically significant reductions in viable aerosolized bacteria from 91.3 to 94.1% during the procedure. These reductions were seen whether the aerosol-producing procedure was performed soon after rinsing, or 40 minutes after

[8] Fine DH, Mendieta C, Barnett ML et al. Efficacy of preprocedural rinsing with an antiseptic in reducing viable bacteria in dental aerosols. J Periodontol 63: 821-824, 1992.

[9] Fine DH, Yip J, Furgang D et al. Reducing bacteria in dental aerosols: Pre- procedural use of an antiseptic mouthrinse. J Am Dent Assoc 124: 56-58, 1993.

[10] Fine DH, Furgang D, Korik I et al. Reduction of viable bacteria in dental aerosols by preprocedural rinsing with an antiseptic mouthrinse. Am J Dent 6: 219-221, 1993.

rinsing with non-aerosol-producing procedures performed in the interim. The use of pre-procedural rinsing was intended as a component of an office infection control regimen aimed at controlling the level of viable bacteria in the dental operatory. The concept of including pre-procedural rinsing in infection control regimens had previously been put forward in a publication ("State-of-the-art infection control in dentistry," Cottone, JA, Molinari, JA, *J Am Dent Assoc* 1991; 122:33-41) and in recommended guidelines for dental school clinics ("Recommended clinical guidelines for infection control in dental education institutions, *J Dent Educ* 1991; 55:621-627).

The Subcommittee discussed the submission at its October 22, 1998 meeting. It was recognized that, while pre-procedural rinsing with Listerine Antiseptic mouthrinse had a significant effect on viable aerosolized bacteria, studies demonstrating that this would in turn reduce disease transmission had not been conducted. Indeed, feasibility and ethical considerations might well preclude the conduct of such a study. Accordingly, it was agreed that the professional indication should be accompanied by the phrase: "Effect on disease transmission not determined." Dr. Linda Katz from the FDA noted that this would be analogous to the inclusion of the caveat: "The clinical relevance of this is unknown" in prescription labeling. The Subcommittee, however, voted not to accept this professional labeling claim intended exclusively for dental professionals.

We hereby request that the FDA consider this issue for several reasons. First, the clinical studies cited above and submitted to FDA clearly demonstrate the effectiveness of preprocedural rinsing with the essential oil-containing mouthrinse in significantly reducing the level of viable aerosolized bacteria for meaningful time periods. Second, in

addition to the earlier recognition of a role for preprocedural rinsing in infection control regimens, two other organizations have supported this procedure in more recent recommendations. In its "Infection Control in Dentistry Guidelines," the Office of Safety and Asepsis Procedures Research Foundation states in Section 4, Mouth Rinses:

> A pre-procedure mouth rinse should be used to reduce the number of microbes in the patient's mouth. The mouth rinse should have residual activity to help maintain reduced microbial levels throughout the appointment.

In its July 2, 2003 draft update of its Recommended Infection Control Practices for Dentistry, the U.S. Centers for Disease Control and Prevention states that:

> studies have shown that a pre-procedural rinse with a long-lasting antimicrobial (e.g., chlorhexidine gluconate, essential oils, povidone-iodine) can reduce the level of oral microorganisms generated during dental procedures with rotary instruments (e.g., dental handpieces, ultrasonic scalers).....Pre-procedural mouth rinses may be most beneficial before a procedure using a prophylaxis cup or ultrasonic scaler because rubber dams cannot be used to minimize aerosol and spatter generation; unless the provider has an assistant, high-volume evacuation is not commonly used.

Additional evidence supports the effectiveness of the essential oil-containing mouthrinse in producing significant reductions in salivary bacteria for up to 5 hours[11,12].

Thus, clinical studies clearly support the effectiveness of rinsing with the essential oil-containing mouthrinse in significantly reducing the level of viable aerosolized bacteria during dental procedures and the usefulness of preprocedural rinsing as a component of a dental office infection control regimen is now well accepted. As it is not uncommon for professional labeling to be included in FDA OTC drug monographs, we

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[11] DePaola LG, Minah GE, Overholser CD et al. Effect of an antiseptic mouthrinse on salivary microbiota. Am J Dent 9: 93-95, 1996.

request that FDA consider this issue and, in view of the data and current practice, include a section on professional labeling for the fixed combination of essential oils in the monograph. The professional labeling should include the indication: "For the reduction of viable aerosolized bacteria during dental procedures" and could also include a caveat such as: "Effect on disease transmission not determined."

IV. Corrections to the Essential Oils Effectiveness Section in the Panel Report

For the record, we are submitting the following editorial changes to the panel report section on the effectiveness of the fixed combination of essential oils (68 Fed. Reg. at 32252-56) to correct factual errors and reflect consistency in the presentation of study results:

> 68 Fed. Reg. at 32252, third column, last paragraph: In the first sentence, "seven" should be changed to "eight", the number of studies ultimately reviewed by the Committee.
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> 68 Fed. Reg. at 32253, first column, last paragraph: The mean gingival indices listed are not correct and not consistent with Table 5. The first sentence should read, "Mean gingival index scores for the 127 subjects who completed 6 months of the study were as follows: 1.31 for the essential oil group, 1.37 for the vehicle control group, and 1.46 for the water control group.
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> 68 Fed. Reg. at 32254, first column, first full paragraph (paragraph under Table 6): To be consistent with the presentation of the results of the previous study, a sentence should be inserted at the start of the paragraph as follows: "At 6 months,

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[12] Jenkins S, Addy M, Wade W et al. The magnitude and duration of the effects of some mouthrinse products on salivary bacterial counts. J Clin Periodontol 21: 397-401, 1994.

the essential oil mouthrinse gingival index score was statistically significantly lower than the control by 34%."

68 Fed. Reg. at 32254, third column, second paragraph (paragraph under table 6): The sentence, "The specific teeth used were not cited in this report" should be changed to, "Supragingival plaque was collected from all four first molars (or, if absent, from the adjacent tooth)."

68 Fed. Reg. at 32254, third column, last paragraph (paragraph under Table 8): The words "a statistically significant" should be inserted as follows: "...at 6 months showed a score for the essential oils (0.90) that was a statistically significant 22.4% less than the control score (1.16)."

68 Fed. Reg. at 32255, Table 10, "Group" column: "Essential Oils Plus Mint" should be changed to "Chlorhexidine Gluconate."

68 Fed. Reg. at 32255, third column, second paragraph (paragraph under Table 10): The last sentence should read "Both active groups were statistically significantly different from the control at 6 months."

68 Fed. Reg. at 32255, first column, second paragraph from bottom (paragraph under Table 11): The second sentence should be revised to read, "The results showed that the mean gingival index scores and mean bleeding index scores for the essential oil and the essential oil variant groups were statistically significantly lower than the control group at 6 months, with respective percent gingival index score reductions of 21.4% and 23.3%."

68 Fed. Reg. at 32255, third column, last paragraph: The second sentence should read, "Some of these studies used younger populations weighted with dental students."

In accordance with these comments we are requesting that FDA:

- Conclude that oral care product claims associated only with the cosmetic benefits of plaque reduction are solely cosmetic product claims
- In accordance with the scientific rationale presented in Warner-Lambert's April 27,1998 submission to the Subcommittee, require both *in vivo* and *in vitro* final formulation testing of products containing the fixed combination of essential oils
- Review the scientific data and include in the monograph a professional labeling section for the fixed combination of essential oils

- Note the corrections to the panel report section on essential oil effectiveness, and include these in the record

Thank you for your consideration of these comments. Please contact me if you have any questions or require any further information.

Sincerely,

Don Jantzen
Director, Regulatory Affairs