

Attachment 1

Colgate-Palmolive Company
Docket 81N-033P
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Colgate-Palmolive Company

FDA Request for Data and Information: Triclosan

**Oral Health Care Drug Products for Over-the-Counter Human Use;
Antigingivitis/Antiplaque Drug Products**

Attachment 1

**Supplemental Comments on Ciba Specialty Chemicals Corporation's Time
and Extent Application (TEA) for Triclosan**

Supplemental Comments on Ciba Specialty Chemicals Corporation's Time and Extent Application (TEA) for Triclosan

These comments address whether triclosan is eligible to be included in the OTC drug monograph system. As discussed further below, triclosan is not eligible for inclusion in the OTC drug monograph for antigingivitis/antiplaque products because Ciba Specialty Chemicals Corporation's TEA fails to demonstrate that this condition qualifies for the time and extent exclusion from the "new drug" definition in section 201(p), 21 U.S.C. § 321(p). We previously demonstrated, in our comments to this docket dated October 4, 2004, that there are inadequate data supporting "generally recognized as effective" status for triclosan alone for antiplaque/antigingivitis indications.¹

I. Background

Only drugs that are not new drugs may be marketed pursuant to an over-the-counter (OTC) drug monograph. Under the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 355(a), before a "new drug" may be marketed in the United States, a new drug application (NDA) must be submitted to and approved by FDA. The term "new drug" is defined by section 201(p) of the FDCA, 21 U.S.C. § 321(p), to mean:

(1) Any drug * * * the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, * * *
or

(2) Any drug * * * the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

The courts have interpreted section 201(p) to mean that, to avoid new drug preapproval requirements, a drug must be generally recognized as safe and effective (GRAS/E) and must have been used to a material extent and for a

¹ As further support for our October 4, 2004, comments, we are enclosing with this submission the July 25, 2005, opinion of Michael L. Barnett, D.D.S., regarding the importance of product formulation for the effectiveness of oral care products containing triclosan. Dr. Barnett's opinion supports both our contention that triclosan is not generally recognized as effective and our assertion that Ciba has not satisfied the threshold eligibility criteria in FDA's TEA regulations. See *infra* Attachment 2.

material time under the labeled conditions of use. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 631 (1973); Premo Pharmaceutical Labs., Inc. v. United States, 629 F.2d 795, 801-802 (2d Cir. 1980).² Thus, to be eligible for inclusion in the OTC drug monograph system, a drug must satisfy the time and extent criteria of section 201(p).³

Historically, FDA took the position that only marketing experience in the United States could be used to satisfy the statutory time and extent criteria. 69 Fed. Reg. 51,625, 51,626 (Oct. 3, 1996). In 1996, FDA published an advance notice of proposed rulemaking (ANPR) seeking comment on whether to amend its regulations to address how OTC marketing experience in the United States or abroad could satisfy the time and extent criteria. 69 Fed. Reg. at 51,625. FDA published a proposed rule on December 20, 1999. 64 Fed. Reg. 71,062.

The final regulations were published in the Federal Register on January 23, 2002. 67 Fed. Reg. 3,060 (codified at 21 C.F.R. § 330.14). The regulations permit "conditions" without any marketing experience in the United States to become eligible for FDA's OTC drug monograph system. The term "condition" means an active ingredient or botanical drug substance (or a combination of active ingredients or botanical drug substances), dosage form, dosage strength, or route of administration, marketed for a specific OTC use. 21 C.F.R. § 330.14(a). For a condition to become eligible for consideration in the OTC drug monograph system, a time and extent application (TEA) must be submitted to FDA demonstrating that the condition meets the time and extent criteria set forth in 21 C.F.R. § 330.14(b) & (c). If, after reviewing the TEA, FDA finds that the condition has been marketed OTC for at least five continuous years in the same country and in sufficient quantity, 21 C.F.R. § 330.14(b), the agency publishes a notice of eligibility and request for safety and effectiveness data for the proposed OTC use.

On November 25, 2003, Ciba Specialty Chemicals Corporation (Ciba) submitted a TEA for triclosan, both alone and in combination, as an antigingivitis active ingredient in dental pastes and oral rinses. On July 6, 2004, FDA published a notice of eligibility and request for data and information announcing FDA's determination that triclosan, 0.3 percent maximum, as an antigingivitis ingredient in dental pastes and oral rinses is eligible for inclusion in the OTC oral health care drug products monograph. 69 Fed. Reg. 40,640. FDA also requested that interested persons submit

² FDA confirmed this interpretation in the advance notice of proposed rulemaking for the TEA regulations, published on October 3, 1996 (61 Fed. Reg. 51,625, 51,626).

³ Because of the public health importance of FDA review of new drugs, the courts have held that the "new drug" definition is to be interpreted broadly. See, e.g., Premo Pharmaceutical Labs., Inc. v. United States, 629 F.2d 795, 802 (2d Cir. 1980).

data and information to assist the agency in determining whether triclosan is GRAS/E.

On October 4, 2004, Colgate-Palmolive submitted comments in response to FDA's July 6, 2004, notice. These comments demonstrated that there are inadequate data supporting GRAE status of triclosan alone for antiplaque and antigingivitis indications. In the accompanying cover letter, Colgate-Palmolive advised FDA that supplemental comments would be submitted later. By letter dated April 18, 2005, FDA advised Colgate-Palmolive that these additional comments would be accepted if submitted before FDA completed its review of the October 4, 2004 comments. We are now submitting supplemental comments.

Our October 4, 2004 comments primarily addressed whether triclosan is GRAE as an antigingivitis active ingredient in dental pastes and oral rinses. These supplemental comments focus on the eligibility of triclosan for inclusion in the OTC drug monograph system. As discussed further below, triclosan is not eligible for inclusion in the OTC drug monograph for antigingivitis/antiplaque products because Ciba's TEA fails to demonstrate that this condition satisfies the time and extent criteria in section 201(p).

II. Argument

To demonstrate eligibility, Ciba relies on foreign marketing experience with products that contain triclosan in a unique delivery system or triclosan in combination with other active ingredients. Ciba has submitted no time and extent data demonstrating that triclosan has been marketed for a material time and to a material extent in the United States or abroad as the lone active ingredient in a conventional oral health care delivery system of the type that will likely be permitted under the final monograph for both antiplaque and antigingivitis indications. Accordingly, triclosan is not eligible for inclusion in the OTC drug monograph system and is a "new drug" under section 201(p) for which an NDA must be submitted.

A. Ciba's TEA

In its TEA, Ciba proposed triclosan up to 0.3 percent for inclusion as an active ingredient alone and in combination with other active ingredients, e.g., sodium fluoride, in the antigingivitis/antiplaque drug products monograph. To demonstrate time and extent, Ciba contends that its brand of triclosan has been marketed over the counter for oral care use for at least five continuous years in 14 of those countries.⁴

⁴ In Table 1 of the TEA, Ciba lists 16 countries in which triclosan has been "sold or marketed for five continuous years or more." The reason for the numerical discrepancy is unknown to Colgate-Palmolive.

Ciba also pointed out that triclosan has been marketed in the United States for oral care under an approved new drug application (NDA) for six years.⁵

B. Inadequacy of Marketing Experience Data Supplied by Ciba

Ciba's TEA fails to demonstrate that triclosan has been marketed for a material time and to a material extent within the meaning of section 201(p) because it relies almost exclusively on marketing experience with products in which triclosan is part of a unique formulation or is one of two active ingredients.⁶

1. Colgate Total®

The marketing of triclosan in Colgate Total® Toothpaste does not support Ciba's TEA. Colgate Total® contains a patented co-polymer that helps the dentifrice remain active between brushings. In our October 4, 2004 comments, we explained that triclosan must be carefully formulated in an appropriate vehicle to be clinically effective. Triclosan possesses moderate antibacterial activity alone. Accordingly, researchers have sought ways to enhance the antiplaque and antigingivitis effectiveness of triclosan over and above its effectiveness alone.

The addition of the co-polymer to triclosan in Colgate Total® significantly increases uptake of triclosan to hydroxyapatite and to gingival tissue. Clinical studies have shown that elevated levels of triclosan are retained in the oral cavity between tooth brushing occasions and that these elevated levels provide sustained reductions in plaque viability throughout these periods, contributing to a reduction in plaque and gingivitis. Other aspects of the formulation, such as the surfactant concentration, are also important to the clinical efficacy of this formula. Put another way, the effectiveness of triclosan is highly dependent on formulation.

⁵ This is a reference to Colgate-Palmolive's NDA for Colgate Total® Toothpaste, an OTC dentifrice containing triclosan and sodium fluoride and approved by FDA in 1997 as an aid in the prevention of cavities, plaque, and gingivitis. As discussed in detail *infra*, marketing experience with Colgate Total® does not support Ciba's TEA because the triclosan in Colgate Total® is delivered through a unique formulation, and because triclosan is not the only active ingredient in the product.

⁶ Ciba identifies but a single product – a Colgate-Palmolive brand of mouthrinse marketed in South Africa – that contains triclosan as the lone active ingredient.

FDA has recognized, in a variety of contexts, the importance of formulation to safety and effectiveness (and to GRAS/E status). In 1983, FDA learned that E-Ferol, a single active ingredient vitamin E aqueous solution intended for intravenous use, was associated with the deaths of premature infants. Because oral and intramuscular forms of vitamin E have previously been marketed without FDA approval, the manufacturer did not seek FDA approval of the aqueous form, and FDA did not request such approval. After receiving reports from the Centers for Disease Control and Prevention (CDC) that the aqueous formulation of the drug had been associated with the deaths of premature infants in some States, FDA revised its compliance policy to indicate that FDA may take immediate enforcement action against new or changed versions of unapproved prescription drug products that are similar or related to, but different from, a pre-1962 product whose regulatory status is unresolved. See 49 Fed. Reg. 38,190 (Sept. 27, 1984); Compliance Policy Guide 7132c.02.

FDA action on guaifenesin also supports Colgate-Palmolive's position on the importance of formulation. On July 12, 2002, consistent with FDA's general requirement of premarket approval for all extended-release formulations of drugs, FDA approved an NDA for a single-ingredient guaifenesin 600 milligram extended release drug product. See FDA, FDA Proposes Steps to Assure the Safety and Efficacy of Certain Currently Unapproved Medicines (Oct. 17, 2003) (news release) (<http://www.fda.gov/bbs/topics/NEWS/2003/NEW00962.html>). Several months later, the Agency sent warning letters to the manufacturers of single-ingredient guaifenesin extended release products that were not covered by approved NDAs or ANDAs. Id. In October 2003, FDA issued a draft guidance document encouraging manufacturers of "old," unapproved drugs to obtain FDA approval. 68 Fed. Reg. 60,702 (Oct. 23, 2003). In issuing the draft, FDA noted that immediate release guaifenesin would continue to be widely available over-the-counter. FDA thus clearly distinguished between two formulations of guaifenesin, just as FDA should do with respect to triclosan.

Moreover, the triclosan in Colgate Total® is combined with another active ingredient: sodium fluoride. As discussed below, marketing experience with this combination cannot be used to satisfy the time and extent criteria in section 201(p).

2. **Dual-Active Products**

Neither does the other marketing experience cited by Ciba support the eligibility of triclosan for the monograph. According to Table 1 of Ciba's TEA (Attachment 3), triclosan has been sold or marketed for at least five continuous years in fifteen countries (in addition to the United States, where triclosan is marketed under the approved NDA for Colgate Total® Toothpaste). Ciba's Table 4 (Attachment 3) does not identify the specific triclosan-containing products marketed in five of those countries. In none of the remaining ten countries has triclosan been marketed as the sole active ingredient in a dentifrice, as shown in the Table A below.

Table A: All Foreign Marketing Experience Included in Ciba's TEA for Triclosan (Dentifrices Only)

Products	Active Ingredients	Triclosan Sole Active Ingredient?
<i>Australia</i>		
GSK Macleans Active Toothpaste	Triclosan, sodium fluoride	NO
Colgate Total		
Dua Protection Sensodyne		
Cedel Whitening Toothpaste		
<i>Brazil</i>		
BBP Comercio e Distribuidor Ultra Action Total Toothpaste	Triclosan, sodium fluoride	NO
<i>China</i>		
Crest tea fresh toothpaste	Triclosan, tea extract, fluoristat	NO
Crest many-in-one toothpaste	Triclosan, Chinese herbs	
Colgate Total Plus Whitening Toothpaste	Triclosan, sodium fluoride	

Table A (Continued): All Foreign Marketing Experience Included in Ciba's TEA for Triclosan (Dentifrices Only)

Products	Active Ingredients	Triclosan Sole Active Ingredient?
France		
Colgate Total toothpaste	Triclosan, sodium fluoride	NO
Kisby Bucco Natural toothpaste		
Unilever Signal Integral		
Germany		
Dr Scheller Durodont 5 Medical Fresh & White toothpaste	Triclosan, sodium fluoride	NO
Procter & Gamble Blend-a-med complete-plus		
India		
Church & Dwight Lever Home/Mentadent Super 6 Complete Care Toothpaste	Triclosan, sodium fluoride, vitamin E	NO
Italy		
Unilever Mentadent P	Triclosan, zinc citrate, sodium fluoride	NO
Colgate Total	Triclosan, sodium fluoride	
GlaxoSmithKline Iodosan Protezione Globale		
Mexico		
Colgate Total	Triclosan, sodium fluoride	NO
Crest Multi Protezione Menta Fresca		
South Africa		
Colgate Total	Triclosan, sodium fluoride	NO
United Kingdom		
Colgate Total	Triclosan, sodium fluoride	NO
Aquafresh		
Signal Integral ⁷		

The distinction between single-active and dual-active products matters. An "active ingredient" is, according to FDA's own regulations (21 C.F.R. § 60.3(b)(2)), "a component of a drug that is intended to furnish pharmacological activity or other

⁷ We understand that Signal Integral was never marketed in the United Kingdom. It cannot, therefore, support Ciba's TEA.

direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body," even if the component is changed chemically in manufacturing and is present in the finished product only in modified form. The linchpin of the definition is whether the component is intended to furnish direct drug effect.

Because, by definition, active ingredients have this effect, they can interact in clinically important ways when combined. That is why 21 C.F.R. § 310.3(h)(2) makes clear that a drug lawfully marketed under an OTC monograph becomes a "new drug" for which an NDA is required if a new active ingredient is added to it. United States v. Promise Toothpaste, 826 F.2d 564, 566 (7th Cir. 1987) ("new combinations of well-known drugs constitute new drugs for purposes of the Act exactly because the effects of drugs in combinations are often not the sum of their parts") (quoting United States v. Articles of Food and Drug . . . Coli-Trol 80, 518 F.2d 743, 746 (5th Cir. 1975)); see also 21 C.F.R. § 330.10(a)(4)(iv) ("An OTC drug may combine two safe and effective active ingredients and may be generally recognized as safe and effective. . . when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients. . . .").

FDA applied this principle specifically in the TEA rulemaking. According to the preamble accompanying the TEA final rule (67 Fed. Reg. at 3,068), a comment on the proposed rule:

expressed concern that the proposed eligibility criteria would require the submission of an NDA or TEA for even a slight variation of a monograph product. The comment cited examples that could trigger the requirement of an NDA or TEA, such as a simple combination of two well established OTC drug ingredients The comment argued that a condition not authorized by a final monograph is not automatically a "new drug" and the agency has the discretion under 21 CFR 310.3(h), to recognize that not all new conditions make a product "new."

FDA responded:

A combination of two well established OTC drug ingredients that is not included in an existing OTC drug monograph or that has not been marketed in the United States would need a TEA. If one of the ingredients is marketed under an NDA, the product is considered a new drug and the combination would need an NDA.

The distinction between single-active ingredient drugs and dual-active ingredient drugs also explains why the general combination policy for antigingivitis/antiplaque drug products adopted by the Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee recognizes that combinations can change the safety and effectiveness of individual ingredients. 68 Fed. Reg. 32,232, 32,240 (May 29, 2003).

FDA's policy is so well-established in this area that the agency actually initiated enforcement action in a closely analogous context where a drug active ingredient was marketed as part of a combination product. Beginning in 2000, FDA sent letters to manufacturers of combination drug-dietary supplement products advising them of the agency's "serious concerns about the marketing" of such products. According to the letters:

These types of combination products raise a number of significant public health and policy issues. For example, the addition of a new ingredient to a legally marketed drug product could affect the safety and efficacy of the drug component. . . . Until the agency has carefully considered these issues . . . , FDA strongly recommends that firms refrain from marketing products that combine both drug and dietary supplement ingredients (except for products marketed under an approved new drug application).

See Letter from Margaret M. Dotzel, Assoc. Comm'r for Policy, to James Ascher, Sr., Pres. & CEO, B.F. Ascher & Co., Inc. 1 (May 30, 2000) (available at <http://www.cfsan.fda.gov/~dms/dspltr02.html>) (emphasis

added); see also Letter from Margaret M. Dotzel, Assoc. Comm'r for Policy, to Kathleen M. Sanzo, Esq. & Phoebe Mounts, Ph.D., J.D., Morgan Lewis & Bockius 1 (May 30, 2000) (available at <http://www.cfsan.fda.gov/~dms/dspltr03.html>); Letter from Margaret M. Dotzel, Assoc. Comm'r for Policy, to David F. Nolte 1 (May 30, 2000) (available at <http://www.cfsan.fda.gov/~dms/dspltr04.html>).

The following year, FDA sent warning letters to two firms objecting to the marketing of combination drug-dietary supplement products. According to these letters, the products are "new drugs" under section 201(p) of the FDCA and 21 C.F.R. § 310.3(h). Importantly, the warning letters specifically stated that the products were ineligible for the OTC drug monograph system because no other product formulated with these active ingredients had ever been marketed:

[T]hese products are not generally recognized as safe and effective for their respective labeled uses. Neither of these products is subject to the Food and Drug Administration's (FDA's) Over-The-Counter (OTC) Drug Review because no other product formulated with these active ingredients and labeled for these intended uses has ever been commercially marketed, and the agency has never proposed that such a product be included in this Review. Thus, these . . . products violate section 505(a) of the Act because they are new drugs and neither is the subject of an approved New Drug Application (NDA).

Letter from David J. Horowitz, Esq., CDER to Klee Irwin, Pres. & CEO, Omni Nutraceuticals, Inc. 3 (Oct. 16, 2001); Letter from David J. Horowitz, Esq., CDER, to James Ascher, Sr., Pres. & CEO, B.F. Ascher & Co., Inc. 3 (Oct. 16, 2001). As these actions demonstrate, FDA is so keenly aware of the potential safety and effectiveness implications of adding a drug active ingredient, that it applies this principle even to non-drug substances, such as dietary supplements.

As we have demonstrated, it is inappropriate for FDA to rely on marketing experience with Colgate Total®, which contains

triclosan in a unique formulation, or with any other triclosan product containing an additional active ingredient. As FDA has repeatedly and consistently recognized for many years, the formulation of a drug product or the combination of one active ingredient with another can have substantial implications for safety and effectiveness. Marketing experience with the products identified by Ciba is not pertinent to FDA's determination of whether triclosan has been marketed for a material time and to a material extent within the meaning of FDA's TEA regulations. FDA should therefore find that Ciba's TEA does not satisfy the time and extent criteria in Section 201(p).

III. **Fundamental Fairness Precludes Triclosan's Eligibility**

FDA's TEA regulations contemplate a two-step procedure for including a new condition in the OTC drug monograph system. First, the proponent of the new condition submits a TEA demonstrating that the condition is eligible based on the time and extent criteria of section 201(p). Second, if FDA agrees with the proponent that the condition is, indeed, eligible for inclusion in the OTC drug monograph system, FDA publishes simultaneously in the Federal Register a notice of the eligibility determination and a request that interested parties submit data and information relevant to GRAS/E status. See 21 C.F.R. § 330.14.

The proponent's TEA is not disclosed to the public until FDA decides that the condition is eligible and publishes its notice in the Federal Register. In such notices, FDA specifically requests submissions of data and information on GRAS/E status, but does not expressly submit the eligibility determination to public scrutiny. Consequently, interested parties have no meaningful opportunity to comment on the eligibility determination. Such opportunity must be afforded under the Administrative Procedure Act (APA), 5 U.S.C. § 553.

Whatever the legality of the TEA regulations under the APA, here, interested parties had even less opportunity to participate in the process of including triclosan in the OTC drug monograph system. In 2003, FDA published its conclusion, based on the recommendation of the Subcommittee, that triclosan was not eligible for inclusion in the OTC drug review because it was not marketed for a material time and to a material extent for antigingivitis/antiplaque use in the United States. 68 Fed. Reg. 32,232, 32,235 (May 29, 2003). The agency afforded interested parties no notice before issuing the July 6, 2004, notice reversing its 2003 decision and seeking GRAS/E data. 69 Fed. Reg. at 40,640 ("The condition triclosan, 0.3 percent maximum, as an antigingivitis ingredient in dental pastes and oral

rinses will be evaluated for inclusion in the monograph being developed for OTC oral health care drug products (21 CFR part 356)."). Worse than providing no notice, here FDA specifically found that triclosan would not be included in the monograph system, only to reverse itself the following year without following prescribed procedures for effectuating the change. Alaska Prof. Hunters Ass'n v. FAA, 177 F.3d 1030, 1035-36 (D.C. Cir. 1999).

Colgate-Palmolive believes that the TEA procedure must provide interested parties with a meaningful opportunity to comment on the eligibility determination before FDA publishes any request for data and information on GRAS/E status of a new condition. In the present case, Colgate-Palmolive not only had no such opportunity, but also reasonably relied on FDA's earlier published determination that triclosan would not be included in the OTC drug monograph system. Colgate-Palmolive therefore requests that FDA reconsider this aspect of the TEA regulations and re-publish the eligibility determination for triclosan to afford all interested parties a meaningful opportunity to comment.

IV. Conclusion

Ciba has not demonstrated that triclosan satisfies the criteria set forth in 21 C.F.R. § 330.14(b) to be considered for inclusion in an OTC drug monograph. Ciba demonstrates, at most, that triclosan has been marketed in antiplaque/antigingivitis products in combination with other active ingredients. Accordingly, FDA should not include triclosan as an antigingivitis ingredient in dental pastes and oral rinses in the monograph being developed by FDA for OTC oral health care drug products.