

Docket No. 81N-0033P

**Over-the-Counter Drug Products;
Safety and Efficacy Review; Additional
Antigingivitis/Antiplaque Ingredient**

**The Procter & Gamble Company
30-September-2004**

**Triclosan
Call-for-Data**

81N-033P

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Procter & Gamble

The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

September 30, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 1981N-0033P, Over-the-Counter Drug
Products; Safety and Efficacy Review; Additional
Antigingivitis/Anti plaque Ingredient

Dear Sir or Madam:

The Procter & Gamble Company (P&G), a leader in the development of dental and oral care consumer products, respectfully submits these comments in response to the call-for-data (*FR Doc. 04-15136*) published in the Federal Register (69 FR 40640) on July 6, 2004, seeking safety and effectiveness information on triclosan, 0.3 percent maximum, as an over-the-counter (OTC) antigingivitis drug ingredient in dental pastes and oral rinses. As the manufacturer of the Crest[®] and Scope[®] family of oral care products, Procter & Gamble has a significant interest in the ongoing development of the OTC Antigingivitis/Anti plaque monograph for which triclosan is now being considered.

P&G has based our comments on four important criteria. First, the Plaque Subcommittee strongly encouraged submission sponsors to explore alternative ways to evaluate the clinical significance of gingivitis clinical trial data as the Subcommittee did not believe a simple statistical difference was adequate. To this end, several additional methods of analysis were requested¹ and presented to the Subcommittee (e.g., statistically-significant reduction in gingivitis, site-specific analysis, subject-based analysis, odds ratio analysis)². The “weight of evidence” from these methods of analysis was subsequently utilized by the Subcommittee to

¹ 68 FR 32248, 32250, 32256

² Docket 1981N-0033P, C-14, Vol. 81 (P&G submission: pp. 109-119)

recommend cetylpyridinium chloride, essential oils and stannous fluoride as Category 1 antigingivitis agents. This "weight of the evidence" precedence should be utilized as the standard by which all ingredients (including triclosan) are evaluated for inclusion in the Antigingivitis/Antiplaque monograph.

Second, P&G has conducted six double-blind, parallel, randomized, placebo-controlled clinical trials on multiple triclosan-containing dentifrice products representing more than 700 evaluated subjects on triclosan formulations. We have relied on these trial outcomes to draw our conclusions concerning the antigingivitis and antiplaque effectiveness associated with the ingredient triclosan.

Third, the Plaque Subcommittee was concerned about the impact of product formulation on the effectiveness of an active ingredient. They recommended ingredient sponsors provide clinically-validated performance tests for inclusion in the monograph to ensure the availability and activity of the active ingredient in the final product formulation. An established, clinically-validated performance test should be provided for all ingredients considered for inclusion in the monograph, including triclosan.

Fourth, P&G has thoroughly reviewed the established body of literature characterizing the ingredient safety of triclosan-containing products and have relied on these data in addition to our own experiential data to assess both the ingredient and topical oral product safety for triclosan.

Based on these four considerations, P&G concludes the following with respect to the safety and effectiveness of the ingredient triclosan:

- The safety data previously presented to the agency and cited in these comments offer strong support for ingredient safety and safe use of dentifrices and oral rinses containing up to 0.3 percent triclosan.
- The ingredient triclosan is a broad-spectrum oral antimicrobial agent that provides meaningful antiplaque and oral malodor benefits. Numerous clinical trials on multiple

formulations have demonstrated that a 0.3% triclosan containing dentifrice product can provide statistically-significant reductions in plaque and oral malodor.

- Procter and Gamble has conducted six well-controlled, double-blind, parallel, randomized gingivitis effectiveness clinical trials on multiple triclosan-containing dentifrice formulations evaluating over 700 subjects on triclosan. Data from these trials suggest triclosan is modestly effective as an antigingivitis agent; however, it does not meet the effectiveness criteria established by the Plaque Subcommittee for inclusion in the Antigingivitis/Antiplaque monograph. P&G acknowledges a significant body of literature^{3,4,5,6,7,8,9,10,11,12,13,14,15,16,17} supporting the effectiveness of an NDA triclosan

³ Garcia-Godoy F, DeVizio W, Volpe AR, et. al.: Effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: A 7-month clinical study. *Am J Dent*, 3:S15-S26, 1990.

⁴ Cubells AB, Dalmau LB, Petrone ME, et. al.: The effect of a triclosan/copolymer/fluoride dentifrice on plaque formation and gingivitis: A six-month clinical study. *J Clin Dent*, 2:63-69, 1991.

⁵ Deasy MJ, Singh SM, Rustogi KN, et. al.: Effect of a dentifrice containing triclosan and a copolymer on plaque formation and gingivitis. *Clin Prev Dent*, 13:12-19, 1991.

⁶ Bolden TE, Zambon JJ, Sowinski J, et. al.: The clinical effect of a dentifrice containing triclosan and a copolymer in a sodium fluoride/silica base on plaque and gingivitis: A six-month clinical study. *J Clin Dent*, 4:125-131, 1992.

⁷ Denepitiya JL, Fine D, Singh SM, et. al.: Effect upon plaque formation and gingivitis of a triclosan/copolymer/fluoride dentifrice: A 6-month clinical study. *Am J Dent*, 5:307-311, 1992.

⁸ Mankodi S, Walker C, Conforti N, et. al.: Clinical effect of a triclosan-containing dentifrice on plaque and gingivitis: A 6-month study. *Clin Prev Dent* 14:4-10, 1992.

⁹ Lindhe J, Rosling B, Socransky SS, et. al.: The effect of a triclosan-containing dentifrice on established plaque and gingivitis. *J Clin Periodontol* 20:327-334, 1993.

¹⁰ Svatun B, Saxton CA, Huntington E, et. al.: The effect of three silica dentifrices containing triclosan on supragingival plaque and calculus formation and on gingivitis. *Int Dent J* 43:441-452, 1993.

¹¹ Triratana T, Tuongratanaphan S, Kraivaphan P, et. al.: The effect on established plaque formation and gingivitis of a triclosan/copolymer/fluoride dentifrice: A six-month clinical study. *J Dent Assoc Thai* 43:19-28, 1993.

¹² Kanchanakamol U, Umpriwan R, Jotikasthira N, et. al.: Reduction of plaque formation and gingivitis by a dentifrice containing triclosan and copolymer. *J Periodontol* 66:109-112, 1995.

dentifrice product. However, we contend that a database established for a unique formulation does not necessarily provide general recognition of ingredient effectiveness. It is not clear from the published literature what unique formulation conditions and manufacturing controls are necessary for a triclosan dentifrice formulation to provide the magnitude of effectiveness previously recommended by the Plaque Subcommittee. In addition, to our knowledge no clinically-validated performance test has been developed or proposed to predict the antigingivitis effectiveness of a triclosan-containing formulation.

Therefore, based on these conclusions, P&G asserts the ingredient triclosan is not generally recognized as an effective agent for the prevention or reduction of the disease gingivitis and should not be included in the Antigingivitis/Antiplaque OTC drug monograph until such time as: (1) the ingredient can be demonstrated effective, per the Plaque Subcommittee's "weight of the evidence" requirements, in more than a single formulation approved under an NDA; (2) the formulation, manufacturing controls and usage conditions contributing to triclosan effectiveness are identified to help explain the lack of gingivitis effectiveness in published clinical trials, and (3) a triclosan performance test for ensuring final formulation effectiveness is established.

¹³ Renvert S, Birkhed D: Comparison between 3 triclosan dentifrices on plaque, gingivitis and salivary microflora. *J Clin Periodontol* 22:63-70, 1995.

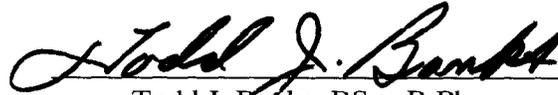
¹⁴ Volpe Ar, Petrone ME, DeVizio W, et. al.: A review of plaque, gingivitis, calculus and caries clinical efficacy studies with a fluoride containing triclosan and PVM/MA copolymer. *J Clin Dent*, 7 Suppl: S1-S14. 1996.

¹⁵ Hu D, Zhang J, Wan H, et. al.: Efficacy if a triclosan/copolymer dentifrice in the control of plaque and gingivitis: A six-month study in China. *West China J Stomatology*, Nov 1997, 15(4): 333-5.

¹⁶ Triratana T, Rustogi KN, Volpe AR, et. al.: Clunial effect of a new liquid dentifrice containing triclosan/copolymer on existing plaque and gingivitis. *J Amer Dent Assoc*, Feb 2002, 133(2):219-25.

¹⁷ Allen DR, Battista GW, Petrone DM, et. al.: The clinical efficacy of Colgate Total Plus Whitening Toothpaste containing a special grade of silica and Colgate total Fresh Strip Toothpaste in the control of plaque and gingivitis: A six-month clinical study. *J Clin Dent* 13(2):59-64, 2002.

We appreciate the opportunity to provide these comments on the ingredient triclosan as it is being considered for inclusion in the developing OTC Antigingivitis/Antiplaque monograph. If Procter & Gamble can be of further assistance, please do not hesitate to contact:



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Appendix A: P&G clinical trials evaluating the therapeutic benefits of triclosan-containing oral care products

1. Triclosan Call-for-Data Background

FDA issued an Advanced Notice of Proposed Rulemaking (ANPR) on May 29, 2003 (68 FR 32231-32287) that established the conditions under which over-the-counter (OTC) drug products for the reduction or prevention of dental plaque and gingivitis are generally recognized as safe and effective and not misbranded. Ciba Specialty Chemicals Corporation (“CIBA”) had previously submitted triclosan data in response to the call-for-data on antigingivitis/antiplaque products, but FDA did not include the ingredient in the ANPR, stating “*some of these ingredients (...including triclosan...) were not marketed for a material time¹⁸ and to a material extent¹⁸ for antigingivitis/antiplaque use in the United States*”¹⁹ and therefore declared the submission “*not eligible for inclusion in the OTC drug review as part of this ANPR and, therefore, are not discussed in this document.*”¹⁹ As a matter of reference, a triclosan-containing dental paste has been approved for marketing in the United States since July 11, 1997 for the prevention of gingivitis (NDA 20231) whereas the Antigingivitis/Antiplaque Panel deliberations concluded on December 3, 1998.

Criteria/Procedures for Classifying OTC Drugs as Safe and Effective – Final Rule

Related to this matter, FDA issued a final rule²⁰ on January 23, 2002 which established the criteria and procedures by which over-the-counter (OTC) conditions may become eligible for consideration in the OTC drug monograph system. The criteria and procedures address how OTC drugs initially marketed in the United States after the OTC drug review began in 1972, and OTC drugs without any U.S. marketing experience, can meet the statutory definition of marketing “to a material extent” and “for a material time” and become eligible. If found eligible, the ingredient would then be evaluated for general recognition of safety and effectiveness in accordance with FDA’s OTC drug monograph regulations.

¹⁸ 21 U.S.C. 321(p)(2)

¹⁹ 68 FR 32235

²⁰ 67 FR 3060 (21 CFR 330.14)

Triclosan Call-for-Data

In accordance with the final rule cited above and during the open comment period following the publication of the Antigingivitis/Antiplaque ANPR, CIBA filed comments²¹ announcing their intention to submit a Time and Extent Application (TEA) to the FDA requesting that triclosan be included in the developing Antigingivitis/Antiplaque OTC monograph on the basis of its long history of use in oral care products. FDA reviewed²² the CIBA TEA and determined that triclosan is eligible for further consideration in its OTC drug monograph system (69 FR 40640). Under this notice of eligibility FDA announced a call-for-data for safety and efficacy information and has stated that triclosan will be evaluated as an antigingivitis ingredient in dental pastes and oral rinses to determine whether this ingredient can be generally recognized as safe and effective (GRAS/E) for its proposed OTC use. The deadline for submitting comments is October 4, 2004.

Effectiveness Criterion Utilized by the Plaque Subcommittee

The Plaque Subcommittee deliberations on antiplaque and antigingivitis ingredients established precedence for two requirements that are relevant to the consideration of triclosan for inclusion in the Antigingivitis/Antiplaque OTC monograph. First, the Plaque Subcommittee worked with ingredient sponsors to define specific effectiveness criteria (weight of the evidence) to establish clinically-significant benefits for Category 1 recommended ingredients.²³ Second, the Plaque Subcommittee worked with ingredient sponsors to establish clinically-validated performance tests to ensure that the availability and activity of Category 1 active ingredients are not attenuated by formulation variables.²⁴ Both of these criteria were deemed necessary for the Plaque Subcommittee to ultimately recommend active ingredients as Category 1 for effectiveness and therefore both of these criteria should be utilized when considering the ingredient triclosan for inclusion in the Antigingivitis/Antiplaque OTC drug monograph.

²¹ Docket 1981N-033P, C-12, Vol. 19, (CIBA submission, dated: November 19, 2003)

²² Docket 1981N-033P, FDA's evaluation and comments on the TEA for triclosan, dated: June 24, 2004

²³ 68 FR 32248 - 32250

²⁴ 68 FR 32240 - 32241

Weight of Evidence Approach for Clinical Significance

During the call-for-data on the Antigingivitis/Antiplaque monograph proceedings, ingredient sponsors submitted data to the Plaque Subcommittee to establish the safety and effectiveness of active ingredients with antiplaque and antigingivitis activity. Because there were no specific FDA guidelines regarding the type or level of effect necessary to establish antigingivitis effectiveness, the Plaque Subcommittee relied on a weight of evidence approach in their determination of effectiveness for each active ingredient. The evidential data utilized by the Subcommittee included first and foremost a statistically significant reduction in gingivitis for the active under consideration relative to its control as determined via a randomized controlled trial of 6-month duration. Additional consideration was given to site-specific analysis, subject-based analysis, and odds ratio analysis. These analyses are briefly described below.

Site-Specific Analysis

While it is recognized that the correct statistical unit of observation is the subject, much can be ascertained regarding the anti-gingivitis effects of chemotherapeutic agents by considering the fate of individual sites within the oral cavity, particularly since the Löe-Silness index assesses gingivitis at up to 168 individual sites surrounding the dentition. Two distinct site-specific analyses provide insight regarding clinical significance. The first is a natural extension of a typical percent reduction analysis and provides information on the degree to which the overall percent reduction is a function of prevention and/or treatment. In this analysis, gingival bleeding is considered more clinically relevant than redness. For each subject at baseline, sites are categorized into bleeding and non-bleeding, based on the Löe-Silness examination. Considering only those sites initially bleeding, the degree to which the chemotherapeutic agent converts these to non-bleeding sites (relative to the control) is a measure of treatment of gingivitis. Likewise, considering only those sites initially non-bleeding, the degree to which the chemotherapeutic agent maintains these as non-bleeding sites (relative to the control) is a measure of prevention of gingivitis. Combined, these outcomes constitute the overall percent reduction in gingival bleeding the test treatment achieves in the clinical trial.

A second site-specific analysis addresses the degree to which a chemotherapeutic agent affords improvements in oral health throughout the gingival tissue by providing information on the site distribution of effectiveness. To do so, the average response at a given site is computed by averaging the Loe-Silness scores for that site from all subjects in a particular treatment group at the end of a clinical study. By comparing the test and control treatments, it is possible to determine the extent to which a chemotherapeutic agent provides its benefit across the dentition. Further, since certain sites are more prone to gingivitis than others, this analysis provides insight into whether or not the active agent is effective at these more susceptible sites. For an effective treatment, it is expected that there will be less gingivitis at the majority of sites in subjects using the test product relative to the control.

Subject-based Analysis

Subject-based analysis provides another approach to assess the clinical significance of a test agent's treatment effect. This analysis involves comparing gingival health at baseline with that observed after some treatment period for individual subjects receiving a test treatment or a control. To perform this analysis, the improvement in overall gingival health from baseline is computed for each subject in a given treatment group. Since each subject typically responds somewhat differently, the distribution in improvement for the active group is compared to that of the control group. For an effective agent, it will be observed that a greater percent of subjects will achieve a larger improvement in gingival health than subjects randomized to the control group.

Odds Ratio Analyses

Another approach to judging clinical significance is odds ratio analyses where the odds of a subject achieving a meaningful improvement in gingival bleeding (defined as at least 50% reduction) from baseline are calculated for subjects in the test group and again for those in the control group. From these, the odds ratios are computed. An odds ratio of 1.0 indicates subjects are just as likely to achieve the improvement in gingival bleeding on the test treatment as on the control while an odds ratio greater than 1.0 indicates subjects in the active treatment group are more likely to receive the benefit than those in the control group. Further, it is possible to perform a meta-analysis of odds ratios from multiple studies investigating the effects of a given

treatment; from this approach, information from all pooled studies can be brought to bear on the question of clinical significance.

Collectively, these means of determining clinical significance (e.g. site-specific analysis, subject-based analysis, and odds ratio analysis) were utilized in an effort to provide a more insightful and thorough assessment than relying on a simple percent reduction analysis. In the end, these types of analyses were conducted on trials for cetylpyridinium chloride, essential oils and stannous fluoride. Each of these three actives were shown to meet the Plaque Subcommittee's expectations for a substantial body of evidence to support the effectiveness of the ingredient.

Performance Testing

Secondly, the Subcommittee was cognizant of the impact diverse formulations can have on the effectiveness of a therapeutic agent(s) and offered the following perspective²⁵:

“Although the OTC drug review is an active ingredient review, not a product review, the Subcommittee recognizes that a final product must be formulated properly, according to accepted pharmaceutical manufacturing practices. If a product is not formulated properly, active ingredients may be present in less than the minimum effective dose, may be in a form that does not exert the intended therapeutic effect(s), or may not be bioavailable.”

To address this concern, the Subcommittee recommended required performance testing of all OTC antigingivitis/antiplaque drug products. This performance testing should be conducted on the product formulation, a standard formulation with effectiveness documented by clinical trials, and a negative control. It was noted that for a product to be considered effective it must demonstrate that it is statistically substantially equivalent to the standard formulation and statistically superior to the negative control as assessed by reasonable statistical analyses.

²⁵ 68 FR 32246

2. General Recognition of Triclosan Safety

Procter & Gamble believes that the safety of triclosan has been adequately demonstrated for topical oral uses at the 0.3% maximum concentration. The safety data, citations and conclusions provided by CIBA in their TEA petition are, in our opinion, a fair and balanced representation of pre-clinical and clinical safety testing. We further acknowledge that the antibacterial agent triclosan, because of its favorable safety profile, has been incorporated into a variety of personal care products, including deodorant soaps, detergents, underarm deodorants, shower gels, and handwashes.

Systemically, pharmacokinetic studies²⁶ have also been conducted to evaluate the bioburden of triclosan in blood and plasma following single-dose and multiple-dose intentional ingestions of a 0.3% triclosan-containing dentifrice. These studies indicate the elimination of a daily triclosan dose is complete and no accumulation is observed when ingesting up to three 1.25g dollops of dentifrice containing 0.3% triclosan.

Additionally, P&G manufactures and markets triclosan-containing dentifrices globally (Asia, Canada, Europe, Latin America) for cosmetic benefits only and in full compliance with the respective governing directives for cosmetic/hygienic oral care products. No disease intervention or antigingivitis drug claims are made for these triclosan-containing dentifrices. Further, as a matter of corporate practice and commitment to our consumers, P&G maintains post-marketing surveillance data on all our consumer products. A review of these data further supports the safe use of dentifrices, up to 0.3 percent triclosan, in a general sales (OTC) environment. No serious adverse reports have been associated with these triclosan dentifrices nor have there been any remarkable adverse reports received.

²⁶ Bagley, DM; Lin, YJ: Clinical evidence for the lack of triclosan accumulation from daily use in dentifrices. *Amer J Dent*, June 2000, 13(3): 148-52

Also noteworthy, the FDA had previously reviewed the ingredient safety of triclosan in a dentifrice indicated for prevention of plaque and gingivitis during the review of NDA number 20231. The findings of the agency, following this review and considering conditions of widespread OTC availability in multiple consumer products (e.g., toothpaste, oral rinses, soaps, detergents, deodorants, shower gels, handwashes, etc.) were that the safety margin was sufficient.

All the available data offer strong support for the ingredient safety and safe use of topical oral products (dentifrices and rinses) containing up to 0.3 percent triclosan in the OTC drug environment.

3. General Recognition of Triclosan Antiplaque Effectiveness

Chemotherapeutic agents represent a valuable complement to mechanical plaque control. The active agent should prevent biofilm formation without significantly affecting the biological equilibrium within the oral cavity. Daily use of an antiplaque agent has been demonstrated to have a positive contribution in promoting gingival health and in preventing disease recurrence by delaying subgingival recolonization by pathogenic micro-organisms.

Triclosan-containing oral care products (dentifrice, rinses, gels) have been extensively tested over the past decade in both human clinical trials^{27,28,29,30,31,32,33} and in *in situ/in vitro* models^{34,35}

²⁷ Grossman E; Hou L; Bollmer BW; et. al: Triclosan/pyrophosphate dentifrice: Dental plaque and gingivitis effects in a 6-month randomized controlled clinical study. *J Clin Dent*, 2002, 13(4): 149-57

²⁸ Triratana T; Rustogi KN; Volpe AR; et. al: Clinical effects of a new liquid dentifrice containing triclosan/copolymer on existing plaque and gingivitis. *J American Dental Assoc*, Feb. 2002, 133(2): 219-25

²⁹ Charles CH; Sharma NC; Galustians HJ; et. al.: Comparative efficacy of an antiseptic mouthrinse and an antiplaque/antigingivitis dentifrice – a six-month clinical trial. *JADA*, May 2001; 132: 670-5

³⁰ Cao C; Sha Y; Meng H; et. al.: A four-day study to evaluate the anti-plaque efficacy of an experimental triclosan-containing dentifrice. *J Clin Dent*, 2001, 12(4): 87-91

³¹ McClanahan SF; Bollmer BW; Court LK; et. al.: Plaque regrowth effects of a triclosan/pyrophosphate dentifrice in a 4-day non-brushing model. *J Clin Dent*, 2000, 11(4): 107-13

³² Hu D; Zhang J; Wan H; et. al.: Efficacy of a triclosan/copolymer dentifrice in the control of plaque and gingivitis: a six-month study in China. *China J Stomatology*, Nov. 1997, 15(4): 333-5

³³ Binney A; Addy M; Owens J; Faulkner J: A comparison of triclosan and stannous fluoride toothpaste for inhibition of plaque regrowth. A crossover study designed to assess carry over. *J Clin Perio*, Mar 1997, 24 (3): 166-70

³⁴ Wu X; Zhang T; Zhang Y: Effect of a new triclosan-containing mouth rinse on oral infection. *Chinese J Stomatology*, Jul 2001, 36 (4): 301-3

³⁵ Guggenheim B; Giertsen W; Schupbach P; Shapiro S: Validation of an *in vitro* biofilm model of supragingival plaque. *J Dent Res*, Jan 2001, 80 (1): 363-70

evaluating the associated antiplaque benefits. Although the treatment effects observed across these tests vary quantitatively (possibly due to differences in measurement technique, study design, or formulation), the overall consensus is that triclosan provides a consistent, relevant effect in plaque prevention. In the judgment of P&G, triclosan is an effective antimicrobial³⁶ agent and when formulated in a topical oral product at approximately 0.3 percent, is capable of providing (and expected to provide) a statistically significant supragingival antiplaque benefit.

³⁶ Baehni PC, Takeuchi Y. Anti-plaque agents in the prevention of biofilm-associated oral disease. *Oral Disease*, 2003, 9 Suppl 1:23-9.

4. Lack of General Recognition that Triclosan Represents an Effective Antigingivitis Agent Based on the Criteria Utilized by the Plaque Subcommittee

CIBA acknowledges in their TEA petition that they have not conducted any plaque or gingivitis clinical effectiveness trials and are relying on established independent and published research to support the efficacy of triclosan. Furthermore, CIBA makes reference to the FDA review and approval of an OTC antigingivitis/antiplaque dental paste containing 0.3 percent triclosan/copolymer (NDA No. 20231) as the primary support of triclosan effectiveness. Moreover, the overwhelming majority of supportive antigingivitis efficacy data cited by CIBA are associated with a single formulation, namely, the NDA-approved triclosan product.

The OTC monograph process is an ingredient-based system that should not be constrained to a unique formulation, whereas the NDA process is limited to a specific formula with specific manufacturing controls. This distinction is relevant in addressing the question of general recognition of triclosan as a monographable antigingivitis/antiplaque agent.

Monograph ingredients should be generally recognized as effective without strong dependence on formulation or process. Clinical testing conducted by Procter & Gamble^{37,38,39,40,41,42}

³⁷ Grossman, E; How, L; Bollmer, BW; et. al.: Triclosan/pyrophosphate dentifrice: dental plaque and gingivitis effects in a 6-month randomized controlled clinical study. *J Clin Dent*, 2002, 13(4): 149-57

³⁸ Lang, NP; Sander, L; Barlow, A; et. al.: Experimental gingivitis studies: effects of triclosan and triclosan-containing dentifrices on dental plaque and gingivitis in three-week randomized controlled clinical trials. *J Clin Dent*, 2002, 13(4): 158-66

³⁹ McClanahan, SF; Bartizek, RD: Effects of triclosan/copolymer dentifrice on dental plaque and gingivitis in a 3-month randomized controlled clinical trial: influence of baseline gingivitis on observed efficacy. *J Clin Dent*, 2002, 13(4): 167-78

⁴⁰ Winston, JL; Bartizek, RD; McClanahan, SF; et. al.: A clinical methods study of the effects of triclosan dentifrices on gingivitis over six months. *J Clin Dent*, 2002, 13(6): 240-8

⁴¹ Cao CF, Sha YQ, Geng SF, et. al.: Reduction of gingivitis in a Chinese population. *J Dent Res Spec Iss* 78: A-

(reprints/abstracts attached in Appendix A) and others^{43,44,45,46,47,48,49} on triclosan-containing dentifrices have repeatedly demonstrated a wide variation in effectiveness, ranging from little or no efficacy to significant reductions in gingivitis.

P&G has conducted four 6-month trials, one 3-month trial and one 21-day Experimental Gingivitis trial evaluating triclosan-containing formulations. These studies evaluated more than 700 subjects on triclosan-containing products. **Table 1** provides a summary of the results reported in these clinical trials (reprints/abstracts attached in Appendix A).

Several of the studies contained positive controls that performed as expected. Particularly troubling is the EG study³⁸ which utilized three cohorts, each representing a different triclosan product preparation (neat dentifrice, 1:3 dilution of dentifrice, and a simple alcoholic rinse formulation [to provide full triclosan solubility/bioavailability]) from which no meaningful

239, 1999.

⁴² McClanahan, SF; Beiswanger, BB; Bartizek, RD; et. al.: A comparison of stabilized stannous fluoride dentifrice and triclosan/copolymer dentifrice for efficacy in the reduction of gingivitis and gingival bleeding: six-month clinical results. *J Clin Dent*, 1997, 8: 39-45

⁴³ Cullinan MP; Westerman B; Hamlet SM; et. al.: The effect of a triclosan-containing dentifrice on the progression of periodontal disease in an adult population. *J Clin Perio*, May 2003, 30 (5): 414-9

⁴⁴ Triratana T; Rustogi KN; Volpe AR; et. al.: Clinical effect of a new liquid dentifrice containing triclosan/copolymer on existing plaque and gingivitis. *JADA*, Feb 2002, 133 (2): 219-25

⁴⁵ Allen DR; Battista GW; Petrone DM; et. al.: The clinical efficacy of Colgate Total Plus Whitening Toothpaste containing a special grade of silica and Colgate Total Fresh Strip Toothpaste in the control of plaque and gingivitis: a six-month clinical study. *J Clin Dent*, 2002, 13 (2): 59-64

⁴⁶ Hu D; Zhang J; Wan H; et. al.: Efficacy of a triclosan/copolymer dentifrice in the control of plaque and gingivitis: a six-month study in China. *West China J Stomatology*, Nov 1997, 15 (4): 333-35

⁴⁷ Binney, AL; Addy, N; Owens, J; et. al.: A 3-month home use study comparing the oral hygiene and gingival health benefits of triclosan and conventional fluoride toothpaste. *J Clin Perio*. Nov. 1996, 23(11): 1020-4

⁴⁸ Volpe AR; Petrone ME; DeVizio W; et. al.: A review of plaque, gingivitis, calculus and caries clinical efficacy studies with a fluoride dentifrice containing triclosan and PVM/MA copolymer. *J Clin Dent*, 1996, 7 Suppl: S1-S14

⁴⁹ Kanchanakamol, U; Umpriwan, R; Jotikasthira, N; et. al.: Reductions of plaque formation and gingivitis by a dentifrice containing triclosan and copolymer. *J Perio*, Feb 1995, 66(2): 109-12

antigingivitis effect was observed. Equally perplexing is the 3-month clinical trial³⁹ which was designed to duplicate the methodology of a previously successful triclosan/copolymer trial. A prospective randomized, blinded, placebo-controlled, parallel group clinical trial was conducted employing the same active product, same clinical site, same clinical investigator and the same gingivitis/plaque examiner used in the successful triclosan/copolymer trial. The trial provided no evidence that the 3-month gingivitis or plaque scores for the triclosan/copolymer group were different from that of the placebo group. Collectively, these data, which represent well-controlled clinical testing of multiple triclosan-containing formulations, do not support a meaningful antigingivitis benefit for the ingredient triclosan.

Table 1: P&G Triclosan Clinical Effectiveness Trials

Citation	Study Duration	Study Population	Test Legs	Anti-plaque Reduction	Antigingivitis Reduction	Gingival Bleeding Site Reduction
37	6-month	186	0.28% TCS/pyro NaF/silica control	13.9% (p<0.01)	-4.0%	-0.6%
38	21-day Exp GI	120	0.28% TCS/pyro	-4.9%	1.3%	6.2%
			0.2% TCS/Zn citrate	-5.5%	-6.3%	-108%
			NaF/silica control	--	--	--
33	0.3% TCS/copolymer 0.28% TCS/pyro NaF/silica control	-3.3%	-7.3%	-2.4%		
		10.5% (p<0.05)	-3.6%	-2.6%		
32	0.12% CHX 0.045% TCS in EtOH CHX placebo TCS placebo	34.8% (p<0.05)	88.2% (p<0.05)	99.7% (p<0.05)		
		-18.1%	12.1%	24.5%		
39	3-month	157	0.3% TCS/copolymer	3.7%	-1.0%	0%
			TCS placebo	--	--	--
40	6-month	256	0.28% TCS/pyro	10.8%	1.5%	-2.0%
			0.3% TCS/copolymer	9.8%	0.3%	6.3%
			NaF/silica control	--	--	--
41	6-month	351	TCS placebo	--	--	--
			0.28% TCS/pyro† NaF/silica control	--	2.5% (p<0.009)	6.8% (p<0.003)
42	6-month	570	0.454% SnF ₂	3.1%	20.5% (p<0.05)	33.4% (p<0.05)
			0.3% TCS/copolymer	0.1%	1.4%	-1.6%
			NaF/silica control	--	--	--

TCS – triclosan, pyro – pyrophosphate, NaF/silica – sodium fluoride dentifrice, MFP/silica – sodium monofluorophosphate dentifrice, CHX – chlorhexidine, EtOH – ethanol

† non-US trial, 1450ppm fluoride

Positive numerical value indicates benefit versus control

Given that P&G and other sponsors^{50,51} have not been successful in showing consistent efficacy in well-established gingivitis models, P&G concludes the ingredient triclosan does not provide a generally recognizable gingivitis benefit that meets the efficacy standards established by the Plaque Subcommittee for inclusion in the OTC drug monograph. One possible explanation is formulation specific effects where the gingivitis benefit is strongly impacted by the product matrix. This cannot be ignored given the evidence that the ingredient triclosan does not demonstrate consistent, effective antigingivitis results across formulations or studies. The majority of successful triclosan clinical trials are associated with testing a single formulation, namely the approved NDA product. If one were to consider the published researched on triclosan, excluding that explicitly associated with the approved NDA product, the clinical effectiveness evidence is insufficient, from a data consistency or magnitude of benefit perspective, to support triclosan as a generally recognized antigingivitis active under the conditions established by this developing monograph. Importantly, it is not clearly understood what the characteristics of a clinically effective triclosan-containing formula are, why the studies by P&G and others demonstrate only limited gingivitis effectiveness, and what clinically-validated performance test can be used to help insure the availability and activity of a triclosan formulation. These questions must be adequately addressed before triclosan can be included in the monograph.

It is the opinion of Procter & Gamble, based on all the available data to date, that the ingredient triclosan does not meet the effectiveness criteria set forth by the Plaque Subcommittee for recognition as an antigingivitis OTC drug agent. Given this lack of general recognition that triclosan-containing oral care products are sufficiently effective in preventing the disease gingivitis, P&G recommends that the ingredient triclosan not be included in the Antigingivitis/Antiplaque OTC drug monograph until such time as: (1) the ingredient can be

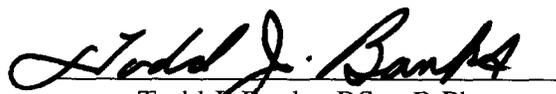
⁵⁰ Nogurira-Filho GR, Toledo S, Cury JA: Effects of 3 dentifrices containing triclosan and various additives. An experiemental gingivitis study. *J Clin Periodontol*, July 2000, 27(7):494-8.

⁵¹ Binney A, Addy M, Ownes J, et. al.: A 3-month home use study comparing the oral hygiene and gingival health benefits of triclosan and conventional fluoride toothpastes. *J Clin Periodontol*, Nov. 1996, 23(11):1020-4.

demonstrated effective, per the Plaque Subcommittee's "weight of the evidence" requirements, in more than a single NDA formulation; (2) the formulation and usage conditions contributing to triclosan effectiveness are identified to help explain the lack of gingivitis effectiveness reported in published clinical trials; and (3) a performance test for ensuring final formulation effectiveness is established.

Lastly, P&G does not support CIBA's request for triclosan to be assigned a Category III status while the agency completes its review and assessment of triclosan. It is our recommendation that the agency not allow OTC marketing of triclosan-containing oral care products for the prevention of gingivitis, in the absence of an approved NDA, since significant questions of antigingivitis effectiveness still remain. Further, we ask that no interim marketing be allowed prior to the agency reaching a final decision on inclusion of triclosan in the monograph.

We are thankful for the opportunity to provide our perspective on the appropriateness of including triclosan as an antigingivitis/antiplaque ingredient under the developing OTC drug monograph. We respectfully ask that the agency give careful consideration to the data and comments contained in this submission. If Procter & Gamble can be of further assistance, please do not hesitate to contact:



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Appendix A
(citations 37 – 42)

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