CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:	**20231**
Trade Name:	**Total toothpaste**
Generic Name:	**Triclosan/sodium fluoride**
Sponsor:	**Colgate-Palmolive**
Approval Date:	**July 11, 1997**
Indication:	**Aids in the prevention of cavities, plaque, and gingivities**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20231

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter	X			X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20231

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-231

Colgate-Palmolive Company
Attention: Paul Okarma, Ph.D., Director, Regulatory Affairs
P.O. Box 1343
Piscataway, New Jersey 08855-7323

JUL 11 1997

Dear Dr. Okarma:

Please refer to your new drug application dated December 29, 1992, received December 30, 1992, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Total Toothpaste (triclosan 0.30% and sodium fluoride 0.24% dentifrice).

Please also refer to our Not Approvable letter dated January 25, 1995, and Approvable letters dated January 31, 1996, and September 5, 1996.

We acknowledge receipt of your submissions dated September 6, 18, and 19, October 7, 8, and 9(2), November 7, 18, 19, and 21, and December 16, 1996; January 13(2), 23, and 28, February 5 and 11, and March 7, May 22 and 28, June 5, 10, and 18, and July 10, 1997. The original User Fee goal date for this application was December 31, 1993. Your submission of January 13, 1997, extended the User Fee goal date to July 13, 1997.

This new drug application provides for the indication of *aids in the prevention of cavities, plaque, and gingivitis.*

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. Marketing the product with FPL that is not identical to this revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-231. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments as specified in your submission dated May 13, 1996. These commitments are listed below:

Protocols, data and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Harold Blatt, Project Manager, at (301)827-2020.

Sincerely yours,

Michael Weintraub

Michael Weintraub, M.D. 7/11/97
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ENCLOSURE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

APPROVABLE LETTER

SEP 5 1996

NDA 20-231

Colgate-Palmolive Company
Attention: Paul Okarma, Ph.D., Regulatory Affairs
P.O. Box 1343
Piscataway, New Jersey 08855-7323

Dear Dr. Okarma:

Please refer to your December 29, 1992, new drug application (NDA) and your resubmissions dated September 29, 1993, July 31, 1995, and March 7, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Total Toothpaste (triclosan 0.30% and sodium fluoride 0.24% dentifrice).

Please also refer to our approvable letter dated January 31, 1996. We acknowledge receipt of your additional communications dated February 7(2), March 6 and 7, April 15, May 13, 14, 28, 30, and 31, June 18 and 25, July 8, and August 7, 16, and 19, 1996.

We have completed the review of this application, and it is approvable. We have several remaining concerns about Total Toothpaste relating to both the OTC target population and the typical toothpaste use-patterns in the OTC population. Before the application may be approved, it will be necessary for you to demonstrate that use of Total Toothpaste would not result in

Draft labeling has not been provided with this letter, since the final label will contain information that will be obtained from either or both of the requested studies.

We remind you of Phase 4 commitments specified in your submission dated July 31, 1995, regarding

. Protocols, data, and final reports should be submitted to your IND for this product, and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements relating to these Phase 4 commitments, must be clearly designated "Phase 4 Commitments".

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding this drug. Please provide updated information as listed below:

Please also update the new drug application with respect to reports of relevant safety information including any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: 1) those involving indications not being sought in the present submission, 2) other dosage forms, and 3) other dose levels, etc.

DMF

Please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days of the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action, FDA may take action to withdraw the application.

This drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions concerning this application, please contact:

Harold Blatt, D.D.S.
Project Manager
Telephone: (301) 827-2020

Sincerely yours,

MW 9/6/96

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-231
HFD-540/Div Files
HFD-540/Dental Files
HFD-2/M.Lumpkin
HFD-80
HFD-105/Weintraub
HFD-40/DDMAC/Raymond
HFD-725/Thomson
HFD-725/~~Acting Team Leader~~/Srinivasan RS 08/13/'96
HFD-540/DIV DIR/Wilkin
HFD-560/DIV DIR/Bowen
HFD-540/CLIN/Hyman FH 8/15/96
HFD-540/CHEM/Vidra ~~JV~~ 8/14/96
HFD-~~160~~ 510/CHEM/Stewart
HFD-540/PHARM/See NAS 8/12/96
HFD-540/PROJ MGR/Blatt DJB 8-12-96
HFD-880/BIOPHARM/Bashaw 8/12/96
HFD-520/MICRO/Altaie
HFD-160/Welch
DISTRICT OFFICE
Concurrence:
HFD-540/DEP DIR/Katz RMH 8/14/96
HFD-725/DIV DIR/Harkins
HFD-540/CHEM SUPV/DeCamp 8/12/96
HFD-540/PHARM SUPV/Jacobs 8/13/96
HFD-520/MICRO SUPV/Sheldon
HFD-880/BIOPHARM SUPV/Bashaw 8/13/96
HFD-540/PROJ MGT SUPV/R.~~Cook~~ 8/12/96
drafted: HB/7-21-96
r/d Initials:
Final

APPROVABLE (AE)

n20231ae.717

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-231

JAN 31 1996

Colgate-Palmolive Company
P.O. Box 1343
Piscataway, New Jersey 08855-7323

Attention: Paul Okarma, Ph.D.
Regulatory Affairs

Dear Dr. Okarma:

Please refer to your December 29, 1992, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Total Toothpaste (Triclosan 0.30% and Sodium Fluoride 0.24% Dentifrice). We also refer to your resubmission dated September 29, 1993.

We acknowledge receipt of your major amendment dated July 31, 1995, which extended the User Fee Due Date to January 31, 1996. We also refer to your amendment dated November 21, 1995.

We have completed the review of this application as submitted with draft labeling, and it is approvable with regards to anti-caries and anti-gingivitis claims. Before the application may be approved, however, it will be necessary to resolve the following issue:

Plaque Claims

Before a claim for plaque reduction can be included in labeling, the significance of plaque reduction must be determined. Unlike gingivitis, plaque, by itself, does not constitute a health outcome. During past meetings, the Dental Products Panel OTC Plaque Products Subcommittee has reached a consensus that plaque and gingivitis claims should be considered together. Published literature, including an article by a task force of experts gathered by the American Dental Association's (ADA) Council on Dental Therapeutics, supports demonstration of a 20% difference in subjects' average gingival indexes between an active control group and a test group to demonstrate clinically significant gingivitis effects. However, we are not aware of published literature that supplies guidelines for a plaque claim.

Although plaque is widely-accepted as a contributory factor to periodontal disease, the exact relationship is unknown. While it is a plausible hypothesis that a statistically significant, but small reduction in plaque (i.e., 10-15%) is directly responsible for a clinically significant reduction in gingivitis (20%), this is only speculative as you have not provided any studies that demonstrate this relationship.

The agenda of the February 29, 1996, meeting of the Plaque Subcommittee of the Dental Products Panel will include as discussion topics: (1) the clinical significance of plaque reduction and its relationship to gingivitis, and (2) gingivitis in children. If you wish to pursue an anti-plaque claim, please submit to the Agency a discussion that supports your position that a clinically relevant reduction in plaque formation has been demonstrated. The recommendations of the Panel will receive careful consideration by the Agency.

We acknowledge receipt of the final report of the carcinogenicity study submitted on January 19, 1996. The study is currently under review by the Agency; please note that this review may result in action that could impact on the marketability and/or labeling of Total Toothpaste.

We remind you of your phase 4 commitments specified in your submission dated July 31, 1995, regarding . Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocols, data, and final reports to this NDA as correspondence. For administrative purposes, all submissions, including labeling supplements relating to these phase 4 commitments must be clearly designated "Phase 4 Commitments".

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that this application is approved.

Should you have any questions, please contact Dr. Roy Blay, Consumer Safety Officer at (301) 827-2040.

Sincerely yours,

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 20-231
HFD-550/Div. Files
HFD-2/MLumpkin
HFD-105/MWeintraub/MJWalling
HFD-80
HFD-550/CSO/R.Blay RB 1/31/96
HFD-550/Bashaw/See/Hyman/Schmidt
HFD-720/Welch
HFD-240 (with draft labeling)
HFD-613 (with draft labeling)
HFD-735/DBarash (with draft labeling)

Drafted: RB/January 31, 1996/20231.004
R/D Init. By:RBlay-1/26/96
F/T by:MMatheny-1/26/96

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

MEDICAL REVIEW(S)

TOTAL™ Toothpaste

(TRICLOSAN/FLUORIDE DENTIFRICE)

NDA #20-231 Amendment

Sponsor: Colgate-Palmolive Company

DENTAL REVIEW
FREDERICK N. HYMAN, D.D.S., M.P.H.
NOVEMBER 1, 1995

Table of Contents

Dental Officer's Review of NDA 20-231
Amendment to Original NDA

Drug:	Triclosan 0.30%, sodium fluoride USP 0.24% dentifrice (Colgate Total™ Toothpaste)	**Serial Number:**	NAZ
		Submission date:	July 31, 1995
		Received date:	July 31, 1995
		Review date:	September 12, 1995
Sponsor:	Colgate-Palmolive Company	**CSO:**	Santford Williams

Proposed indication:
Prevention of plaque, caries and gingivitis

Pharmacologic Category:
Anti-caries, anti-plaque, anti-gingivitis agent

Background

An NDA for this product was reviewed by the Division and resulted in a "not approvable" action of which the sponsor was notified on January 25, 1995. On March 14, 1995, the sponsor replied with a pre-meeting submission (Reply to Letter of January 25, 1995), in which each of the comments from the Agency's non-approval letter was addressed. A meeting was held between the Division and the sponsor on May 22, 1995 during which further discussion transpired. As a result, the sponsor submitted the current document, an amendment to the original NDA, which is very similar to the pre-meeting submission. It consists of several volumes which include a revised point-by-point rebuttal of the Agency's non-approval issues, new study data, publications, and discussion.

The clinical basis for non-approval of the original NDA submission centered around four main issues. The first was the Agency's request for an additional clinical study which supports maintenance of fluoride's anti-caries effect when combined with triclosan; only one acceptable trial was reported previously. Secondly, an OTC status was deemed unacceptable due to several factors: the absence of data supporting efficacy in individuals under the age of 18, the Agency's concern that gingivitis is not a self-diagnosable disease, and the collection of efficacy data only from subjects who began the trial with a professional dental scaling and cleaning. In addition, the Agency was not convinced that the sponsor had demonstrated clinically significant reductions in plaque levels. Finally, in those plaque/gingivitis studies submitted, there were some unresolved questions about the activity of the co-polymer, methyl vinyl ether/maleic acid (PVM/MA).

Executive Summary:

The sponsor has submitted new evidence in this NDA Amendment which supports limited approval of the triclosan/fluoride dentifrice as an OTC anti-caries, anti-gingivitis dentifrice. The anti-plaque claim can still not be approved at this time, as there has not been sufficient evidence to support it. In addition, a phase 4 trial will need to be conducted to demonstrate

Following is a summary of the sponsor's re-submission, grouped by each of the main issues around which non-approval resulted.

1. Anti-caries

In the original NDA submission, the sponsor submitted the results of Trial 1988-5A (Loma Linda), which was accepted as one adequate and well-controlled trial to demonstrate the anti-caries activity of the triclosan/fluoride dentifrice; another caries trial, conducted in Jerusalem, Israel, 1988-6A, was judged to be unacceptable as support for the anti-caries activity of the triclosan/fluoride dentifrice because the level of fluoride tested was 50% greater than the NDA formulation of the test dentifrice. Only the safety data from another anti-caries trial, 0004.90 (Manchester), was submitted. The sponsor objected to the Agency's treatment of the triclosan/fluoride dentifrice as a fixed-combination drug which requires two adequate and well-controlled trials in support of fluoride's anticaries activity; the sponsor submitted copies of past correspondence with the Agency in which substantiation of the anticaries effect of fluoride was discussed. The sponsor asserts that laboratory profile testing as outlined in the Final Monograph for Anti-Caries products is sufficient to demonstrate anti-caries activity. The Division does not agree that prior decisions have conflicted with the current decision regarding meeting the monograph for Anti-Caries products for approval of an anticaries claim. The Division of Over-The-Counter Drugs has not examined possible interactions between triclosan and fluoride. This Division, which is responsible for review of this NDA, considered the evidence concerning fluoride's effect in combination with triclosan, and concluded that there is room for concern.

Nonetheless, in this NDA amendment, the sponsor submitted complete efficacy results from a caries clinical trial conducted on children in Manchester, England, as well as additional data for two adult caries studies that were submitted in the original NDA. The Manchester results acceptably support the anti-caries efficacy of the triclosan/fluoride dentifrice in children. This, coupled with the additional supportive data from Trial 1988-5A in the original NDA submission, demonstrates acceptable anti-caries activity of the product in adults and children.

2. Over-The-Counter Status

The sponsor states that indications for "reduction and prevention" rather than "treatment" of plaque and gingivitis do not require self-diagnosis by the consumer. They submitted summary

minutes of the discussion conducted by the OTC Plaque Subcommittee, during which the group formed the consensus that a reasonable gingivitis claim with appropriate caveats could be used with over-the-counter dental products. In addition, the sponsor submitted three published papers in which human clinical trials without a starting prophylaxis were described and results presented. Although these studies were not designed as pivotal trials, they closely followed the protocol of the pivotal trials, and the results were consistent with the pivotal trial results.

In addition the Agency initially rejected an OTC status for this product because, although limited safety has been demonstrated in youth, neither plaque nor gingivitis efficacy has. The sponsor agrees, and has proposed labelling which is consistent with the new pediatric labeling language regarding lack of efficacy data in children.

3. Clinically Significant Reductions in Plaque

The Agency expressed a concern about an anti-plaque claim due to a lack of evidence for clinical significance of the reductions demonstrated by the pivotal trial data. The sponsor sets forth the motion that a 10% reduction is clinically significant for demonstrating plaque reduction.. but has still not presented compelling evidence to support this statement. The sponsor submitted an unpublished paper by Dr. Sebastien Ciancio entitled: *Clinical Significance of a 20% reduction in Gingivitis* in support of their antiplaque claim. The Agency is in agreement with the conclusion of the paper, that "A 20% reduction in gingivitis is meaningful since it represents a reduction obtained by products accepted by both the American Dental Association, a peer review body, and the Food and Drug Administration, a regulatory body." However, there is no support in Dr. Ciancio's paper for a 10% clinical significance level for *plaque* reduction. Although plaque is widely-accepted an a contributory factor to periodontal disease, it is not the sole etiologic factor; as was discussed with the sponsor previously, the plaque reduction, in fact, does **not** parallel the gingivitis reduction in magnitude or trend in the two pivotal trials. The sponsor has responded by stating that the lack of parallelness between plaque index reduction and gingival reduction is not a discrepancy; they state that the reductions of the indices used were not expected to provide absolute consistency across measurements, but do produce statistically significant and directionally consistent across indices and evaluation intervals. While it is a plausible hypothesis that a small reduction in plaque (i.e., 10%) is directly responsible for a clinically significant reduction in gingivitis (20%), this is only speculative as the sponsor has not provided any studies that demonstrate this. It is the onus of the sponsor of the investigational drug to supply documentation and explanation that supports the assertion of clinical relevance.

4. Activity of co-polymer

One of the sponsor's pivotal studies supported the notion that the co-polymer by itself, has active anti-plaque/gingivitis properties. The sponsor has responded that the co-polymer is

inactive, and has supported this statement with several explanations. The sponsor cautions against making any cross-study comparisons of the absolute magnitude of reductions in plaque or gingival indices. The sponsor also submitted a Federal Register notice (Vol 60, No. 31, February 15, 1995) concerning comments on the use of glycerin in OTC topical otic drug products for the prevention of Swimmer's Ear, which is not compelling evidence since it accepts the premise that glycerine functions only as a vehicle, i.e., without therapeutic activity of its own; this is the very point that the Agency questions.

The sponsor has stated that although they do not feel that additional clinical trials should be required for approval of this NDA, they are willing to commit to the conduct of a Phase 4 clinical trial to further characterize the rententivity contributions of the copolymer in the product.

Reviewer's Recommendation

It is the conclusion of the dental reviewer that the sponsor has responded to the issues that the Agency presented in its non-approval letter for this NDA. The sponsor has indicated a willingness to conduct a Phase 4 trial to clarify the issue of the co-polymer, and to alter labelling where necessary to support OTC indications, and clearly state the lack of efficacy data for gingivitis in children. The anti-plaque claim has not been sufficiently demonstrated and may not be included in the product labelling. As discussed in this review, coupled with the original NDA review, the other claims, including anti-caries, breath freshening, and anti-calculus are acceptable.

In the following sections of the review, new data concerning these four non-approval issues is presented and discussed in detail.

Anti-Caries Trials

Three clinical trials were conducted as a part of this NDA to support the claim that the anti-caries effect of fluoride is not compromised by the addition of the active ingredient triclosan. Trial 0004.90 (Manchester), is discussed in detail since none of the efficacy data was available for review in the original NDA. Data from studies 1988-5A and 1988-6A were submitted in the original NDA, but the Agency asked for additional information regarding these trials. Only the new information pertinent to NDA approval, which was submitted in this amendment, is reviewed here for these two trials.

Demonstrating equivalence claims for anticaries effect

The interpretation of the results for the anticaries trials relied heavily on a publication entitled, *Report of workshop aimed at defining guidelines for caries clinical trials: superiority and equivalency claims for anticaries dentifrices*, published by the Council on Dental Therapeutics of the American Dental Association (See Appendix 5 of the original NDA review dated August 25, 1995 for the entire text). The working group that prepared this document consisted of members of the statistics and dental community who are considered expert in their areas. The guidelines are extremely well thought out, and the discussion that accompanies these guidelines is very cogent. The sponsor submitted a copy of this document in their NDA submission, and relied on it as a guideline for designing the trial and interpretation of results.

In this referenced workshop document, the Council on Dental Therapeutics of the American Dental Association provided recommendations for the conduct of randomized clinical trials to evaluate agents of caries prevention. The guidelines state that two formulations will be considered equivalent if no important clinically significant difference in efficacy can be detected by acceptable methods. Efficacy is measured by two indexes - The Decayed, Missing, and Filled Teeth Index (DMFT) measures the number of decayed and filled teeth that are present in an individual's mouth. At a given time interval, the index is measured again and the increase in value is equal to the incidence of carious teeth (Known as DMFT increment or ΔDMFT). The DMFS is measured in the same fashion, except it considers each of the six surfaces of the tooth as the unit, rather than the tooth. The group agreed that clinical studies aimed at assessing equivalency should be able to detect a 10% difference, with at least 80% power, between the proved clinically effective product (positive control) and the test formulation product. The statistical assessment could be performed by computing the 90% confidence interval for the true difference in efficacy between two products. For equivalency to be established, the absolute value of the upper and lower limits of the 90% confidence interval on the ratio of mean increments must both be within 10% of unity.

<u>Manchester Study</u>

In the original NDA submission, the protocol and safety data for the Manchester caries trial conducted in children was submitted for review; the efficacy results were not provided. In this

amendment, the full results of the trial were provided, including efficacy. The submitted data are discussed in full in the following section.

Summary

The objective of this clinical trial, as stated in the sponsor's protocol was to test the following hypothesis: The 3-year mean caries increment of an at-risk school age population sample, using an 1100 ppm fluoride dentifrice incorporating 0.3% triclosan and 2% co-polymer will be different than that of a similar population sample using an 1100 ppm fluoride positive control dentifrice, *without* 0.3% triclosan/2.0% co-polymer.

This was a single-centered, placebo-controlled, double blind, randomized, two group parallel and single centered clinical trial conducted among 4,060 eleven to thirteen year old schoolchildren who exhibited previous caries experience. It was carried out over the period of three school years (30 months) among schoolchildren in the Greater Manchester, United Kingdom school district. The project involved two dental examiners with mobile road crews covering a total of 45 secondary schools. The examination procedure utilized a visual caries diagnosis technique supplemented by fiber optic transillumination. No radiographs were taken. Product efficacy was determined by comparing DMFS and DMFT scores. Group mean increments, from baseline to interim (fifteen months) examination and baseline to final (thirty months) examination were compared statistically. The final examination results satisfied the pre-set criteria for equivalence of the two groups in terms of new caries experience.

Summary of Patient Participation

A total of 4060 subjects were enrolled in this study. Of these, 598 subjects, consisting of 313 in the triclosan group and 285 in the placebo group, discontinued participation in the study prior to completion. None of the subjects withdrew or dropped from the study for reasons considered by the investigator to be related to the study dentifrice.

Dentifrice	Total Number of Subjects, stratified by gender			Intent to Treat	Completers
	Male	Female	Total	Total	Total
Control	968 (47.7%)	1062 (52.3%)	2030	1842	1745
Triclosan	963 (47.4%)	1067 (52.6%)	2030	1823	1717

Statistical evaluations of the data were performed for both examiners and genders together, as well as by examiner and by gender.

The following table summarizes the reasons for discontinuation. Note that of the two adverse events reported in the triclosan group, both were deaths from automobile accidents. The two adverse events reported in the placebo group were oral ulcerations, one of which was reported by a child who has had a history of oral ulcerations prior to entering the study. It is difficult to discover if adverse events may have contributed to withdrawal for the categories "did not wish to continue", "reason not known", "noncompliance" or "did not return for scheduled exam"; however, since the numbers are very similar for both groups in each reason, it is unlikely that this is the case.

Reasons for Discontinuation

Reason	Triclosan Group Total N = 2030	Placebo Group Total N = 2030
Did not return for scheduled exam	192 (9.5%)	186 (9.2%)
Left school	67 (3.3%)	57 (2.8%)
Did not wish to continue	24 (1.2%)	15 (0.7%)
Noncompliance	9 (0.4%)	7 (0.3%)
Did not like taste	16 (0.8%)	14 (0.7%)
Adverse event, not product related	2 (0.1%)	2 (0.1%)
Reason not known	3 (0.1%)	4 (0.2%)
Total	313 (15.4%)	285 (14.0%)

Formulation

The formulation of the triclosan dentifrice used in the Manchester trial is very similar to the NDA formulation (See following table). There are small differences in concentrations between the two for silica, , and iota carrageenan. The only one of these that could have any impact on dental caries formation is silica, and the 0.5% difference between the two dentifrices is insignificant in that effect. The control dentifrice differs from the triclosan test dentifrice in the absence of triclosan and co-polymer, and sodium hydroxide. There are small differences in the concentrations of silica, , iota carrageenan, and flavor. However, because the control is a commercially available toothpaste, and the objective of the trial is to compare the test dentifrice with triclosan to a commercial fluoride dentifrice for anti-caries effect, the product is acceptable as a comparison.

Comparison of formulations used in Manchester Trial to the NDA formulation

	NDA formulation	Triclosan Dentifrice Used in Manchester Trial	Control Dentifrice Used in Manchester Trial
Ingredient			
Triclosan (Lot # 710216)	0.300		
Sodium Fluoride	0.243		
Deionized Water			
Glycerine USP			
Dental Type Silica NF			
Sodium Lauryl Sulfate			
Flavor (89-242)			
Sodium Hydroxide FCC			
Propylene Glycol USP			
Titanium Dioxide USP			
Iota Carrageenan			
Sodium Saccharin USP			
TOTAL			

Criteria of Effectiveness

To determine effectiveness of the dentifrices, all subjects were evaluated by the same dental examiner (one of two calibrated dentists) at baseline and following fifteen and thirty months of treatment. Missing teeth, sound teeth and tooth surfaces as well as carious teeth and tooth surfaces were recorded onto a computerized examination form using codes which are NIH-approved and universal to caries clinical studies. The examiners also employed fiber optic transillumination light sources to identify posterior interproximal caries lesions and these were regularly validated against each other and a standard light source, to ensure a standard range of light intensity.

Results APPEARS THIS WAY ON ORIGINAL

Dentifrice	Baseline Balance of means for subjects completing study			15-month comparison of means			30-month comparison of means		
	N	DMFT ± SD	DMFS ± SD	N	DMFT ± SD increment	DMFS ± SD increment	N	DMFT increment	DMFS increment
Control	1745	3.64 ± 2.56	5.32 ± 4.50	1842	1.43± 1.82	2.21± 2.93	1745	2.81± 2.54	4.62± 4.70
Triclosan	1717	3.72 ± 2.70	5.48 ± 4.67	1823	1.37± 1.68	2.11± 2.88	1717	2.76± 2.42	4.57± 4.51

Discussion:

The Manchester study results at 15 months failed to satisfy the above recommendations for equivalence. However, at 30 months, the confidence intervals for the pooled DMFT and DMFS data did satisfy the criteria for equivalence. Because statistical testing can only predict the certainty with which *differences* between groups occur, equivalence is an arbitrary outcome. In this case, a 10% cutoff was used to accept equivalence. The 15-month result showed an 11% difference rather than 10% between groups. This does not demonstrate a significant difference between the two groups in terms of caries production. In fact, the 11% difference is in favor of triclosan out-performing the control dentifrice. The 30-month result, which does meet the criteria set forth a priori, is a better gauge of the result, since the group also recommended that caries clinical trials should cover a time period of at least 2 years to draw conclusions. See the statistician's review for more detail about the determination of upper and lower confidence intervals in this trial.

Although radiographs would be helpful as a diagnostic tool, particularly for examination of interproximal decay, it is not necessary, and was not used in the NIDR protocol for their national survey of oral health in U.S. adults and seniors. There is no reason to suspect that

the discovery of interproximal caries would be different between the two groups in this trial. Therefore, the exclusion of dental radiographs does not pose a problem in interpretation of the results.

In conclusion, the Manchester study provides substantial evidence of anticaries efficacy and that the product is safe for use among individuals between the ages of 11 and 18.

Loma Linda Trial (1988-5A)

The following table summarizes the results of Trial 1988-5A, conducted in Loma Linda, California. As discussed above, the criteria for accepting equivalence among the two groups consists of a computing a ratio of new carious surfaces (ΔDMFS) and new carious teeth (ΔDMFT), whose upper limit of confidence is less than 1.10.

Means and Confidence Limits of the ratios of the change in DMFS and DMFT in the triclosan/fluoride dentifrice divided by the fluoride dentifrice at various intervals

	ΔDMFT: Ratio of Triclosan/Fl dentifrice to Fl Dentifrice			ΔDMFS: Ratio of Triclosan/Fl dentifrice to Fl dentifrice		
Interval	Mean	90% Lower Limit	90% Upper Limit	Mean	90% Lower Limit	90% Upper Limit
nths	0.977	0.822	1.160	0.992	0.875	1.125
26 months	0.981	0.840	1.147	1.024	0.906	1.159
36 months	0.926	0.797	1.077	0.958	0.854	1.077
48 months	0.988	0.855	1.141	1.016	0.912	1.131

The a priori hypothesis in the protocol was that the final, 36-month results met the criteria for equivalence, which it does. Note, however, that the 18 and 26-month interim looks, as well as a follow-up look at 48 months have an upper limit that exceeds 1.10. Although it would have been preferable that all of the intervals exhibit a ratio less than 1.1, it is not an inconsistent result. At all intervals, the DMFT ratio is below 1.0, and the DMFS ratio is either 1.0 or less. The trend is actually supportive of a caries rate that is equal to or marginally less with the triclosan/fluoride dentifrice than the dentifrice with fluoride alone. However, for reasons reflective largely of sample size and dropouts, the range in the confidence limit could not be narrowed sufficiently to exclude the possibility that the true means could lie above 1.10. Because the a priori defined result at 36 months does meet the a priori value, and because the interim looks do not contradict the trend, it is an acceptable conclusion that the two products are equivalent in their abilities to prevent caries in an adult population. See the statistician's

review for further discussion of the analysis.

Jerusalem Trial (1988-6A)

The following table summarizes the results of Trial 1988-6A, conducted in Jerusalem, Israel. As discussed above, in order to judge the two groups equivalent in their ability to prevent caries, the upper confidence limit for the ratio of new carious surfaces (ΔDMFS) and new carious teeth (ΔDMFT) expressed as the test group scores divided by the fluoride group scores must be less than 1.10. At each time interval of this trial, the results support the equivalence of the triclosan/fluoride dentifrice to the fluoride dentifrice with respect to their abilities to prevent caries in an adult population. Note that in this trial, the fluoride concentration in the triclosan/fluoride dentifrice is 50% greater than the to-be-marketed fluoride formulation. Because of this, as was discussed in the original NDA review, the results can not be applied with any confidence to the dentifrice with the lower fluoride concentration as submitted for this NDA. The fluoride dentifrice also has this higher level of fluoride, so the conclusion of the study is that the dentifrices are equivalent at a different level of fluoride, which supports the lack of interaction between fluoride and triclosan.

Means and Confidence Limits of the ratios of the change in DMFS and DMFT in the triclosan/fluoride dentifrice divided by the fluoride dentifrice at various intervals

	ΔDMFT: Ratio of Triclosan/Fl dentifrice to Fl Dentifrice			ΔDMFS: Ratio of Triclosan/Fl dentifrice to Fl dentifrice		
Interval	Mean	90% Lower Limit	90% Upper Limit	Mean	90%Lower Limit	90% Upper Limit
18 months	0.877	0.741	1.037	0.945	0.837	1.068
26 months	0.947	0.824	1.090	0.969	0.873	1.075
36 months	0.935	0.822	1.067	0.996	0.914	1.085

For further detail on the statistical analysis, see the statistician's review as well.

OTC Status

During the original submission of this NDA, the Agency had several concerns which prevented the acceptance of this product with OTC status. One overriding concern was the lack of data from subjects under the age of 18 for either the anti-caries or antiplaque/gingivitis claims. We were also concerned that the 20% reductions in gingivitis scores demonstrated with the use of this product more accurately describes treatment than prevention. Another

consideration was that individuals may purchase the product to treat their gingivitis without addressing underlying disease (i.e., periodontitis). Additionally, the trials submitted in the original NDA consisted exclusively of individuals beginning with a professional prophylaxis, causing us to wonder about the effectiveness of the product without that intervention.

Since the time of that initial submission, the sponsor has responded with additional information in support of the product's approval, including a portion of the transcript of the August 14, 1995 meeting of the Plaque Subcommittee of the Dental Products Panel (New Correspondence to NDA, Date Received 10/10/95), the complete results of the Manchester trial, and copies of two published reports of plaque/gingivitis efficacy trials of the product in which subjects were not given a prophylaxis at baseline.

August 14, 1995 meeting of the Plaque Subcommittee of the Dental Products Panel

During this referenced Plaque Subcommittee meeting, the general issue of appropriateness of anti-gingivitis label claims for OTC products was presented to the Plaque Subcommittee for an opinion. The general consensus was that gingivitis is amenable to self-diagnosis and management assuming that the labelling clarifies that use of the product does not take the place of professional care. There was concern raised about delaying dental treatment by developing a false sense of security that because a product was being used for gingivitis, periodontitis is also being treated. However, the public health benefit of providing the use of the product to a large portion of the public by not requiring prescription status was deemed noteworthy. It was also stated that although the label on most OTC products states that if the condition worsens or persists, to visit an professional, another labelling option is to state that they product should only be used after the condition has been diagnosed by a professional.

Appropriateness of this product for children

As was discussed earlier in this review, the Manchester trial provides evidence that the test dentifrice is equivalent to a standard fluoride dentifrice in its ability to prevent dental caries in children ages 11 - 18. The lack of adverse events reported with three years of the dentifrice's daily use also supports the dentifrice's safety in children. However, neither plaque nor gingivitis activity was examined in this trial. In addition, although children develop plaque and gingivitis, its etiology and distribution may be different than for adults. The question then arises as to the need or appropriateness of this product for children. Although the dentifrice appears safe and effective against caries in children, the sponsor's development of this product is for its anti-gingivitis properties. Without adequate demonstration of an anti-gingivitis effect in children, the claims could be misleading. To avoid misleading consumers, the labelling should clearly state that the product has not been tested in individuals under the age of 18 for the gingivitis indication.

The sponsor has proposed labelling which would contain the following statement: "This product has not been shown effective in reduction and prevention of gingivitis in children

under 18 years of age."

According to labeling of drugs regarding pediatric use, Section 201.57 states:

> *(v): If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the "Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (-) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or , if appropriate, the hazard shall be stated in the "Contraindications" or "Warning" section of the labeling and this subsection shall refer to it.*

The sponsor has recorded and submitted a report of adverse events for the three-year trial of 4062 children conducted in Manchester which revealed no findings that would contraindicate its use in children.

Benefits and risks of the product attendant to use over many years.

The Agency also had some question about approving a product that would be used chronically for OTC use; specifically not submitted were data to describe the benefits and risks of the product attendant to use over many years. The sponsor cites Section II.G.(2)(f) of the 1988 Guideline for The Format and Content of the Clinical and Statistical Sections of New Drug Applications:

> "Drugs for chronic use are not usually studied for the full intended period of use, but are generally studied for periods of 6 months to a year."

Although it would be untenable to request data for the full intended period of use (a lifetime), follow-up data for greater than 6 months is warranted. Six months is regarded as the minimum time to determine efficacy of gingivitis/periodontitis products, and given this product's extremely long proposed period of use, this is not an unreasonable request. Long-term efficacy could be evaluated with follow-up of subjects for periods of time greater than one year to determine if the anti-gingivitis effects from this dentifrice persist.

Professional dental prophylaxis prior to using the product

There was also concern that in all of the pivotal trials submitted by the sponsor for the gingivitis indication, the subjects were given a professional supragingival scaling and prophylaxis at baseline. An OTC product would have no way to assure that consumers received a professional dental prophylaxis prior to using the product. The sponsor responded by referencing two published overseas trials that addressed this issue.

One was a 6-month trial of 120 subjects conducted in Thailand in 1993 by Triratana, and the other was a 6-month clinical trial of 110 subjects conducted in Sweden by Lindhe in 1993. Both studies were discussed in an article published by Volpe (*A Review of Plaque, Gingivitis, Calculus and Caries Clinical Efficacy Studies with a Dentifrice Containing Triclosan and PVM/MA Copolymer*, Journal of Clinical Dentistry, Volume IV, Special Issue, p 31-41, 1993). In addition, each trial was published separately (Triratana, *The Effect on Established Plaque Formation and Gingivitis of a Triclosan/Copolymer/Fluoride Dentifrice: A Six Month Clinical Study* , J. Dent. Assoc. Thai. Vol. 43 No. 1 Jan-Feb. 1993, p19-27 and Lindhe, *The effect of a triclosan-containing dentifrice on established plaque and gingivitis*, J. Clin. Periodontol 1993: 20: 327-334). The clinical designs of both of these trials was nearly identical to the five pivotal studies conducted and submitted to this NDA. However, the clinical studies were designed to evaluate the effect of the dentifrice on dental plaque and gingivitis in subjects who received no oral prophylaxis. The entrance criteria were the same, and the subjects were stratified into two balanced groups according to their baseline modified Quigley-Hein Plaque Index and Loe-Sillness Gingival Index scores. Each group was then randomly assigned to use either the dentifrice containing .3% triclosan and 2% of a copolymer in a .243% fluoride/silica base, or a .243% fluoride/silica base placebo dentifrice. All subjects were instructed to brush their teeth twice daily for 1 minute with their assigned dentifrices and soft-bristled toothbrushes provided on regularly scheduled visits. At 6 weeks, and 6 months, the subjects were evaluated by the same dental examiner for plaque and gingivitis scores, which were then computed and analyzed statistically with an Analysis of Variance.

As in all overseas trials, the potential environmental, physical, and cultural differences make the generalizability of the results to U.S. population suspect. In dental studies, diet, access to dental/medical care, and compliance may also be factors which have the potential to affect comparability. As a supporting study, a demonstration on similarity to crucial baseline demographics is necessary to evaluate the results. The following table summarizes baseline characteristics of note:

Baseline Demographics

Comparison of Baseline Demographics of Overseas Trials with U.S. Pivotal Trials 90-TRI-0005 and 90-TRI-0006

	Thai Study	Swedish Study	90-TRI-0005	90-TRI-0006
Gender: % Female	90	to be provided	71	59
Mean Age	31	to be provided	36	32
Gingival Index	1.8	1.5	1.3	1.4
Plaque Index	2.1	2.1	2.4	2.5

Comparison of Gingival Index (GI) and Plaque Index (PI) scores

		Thai Study	Swedish Study	90-TRI-0005	90-TRI-0006
Baseline GI	Triclosan	1.80	1.50	1.29	1.41
	Placebo	1.82	1.60	1.30	1.43
6-Month GI	Triclosan	1.39	1.10	0.94	0.82
	Placebo	1.71	1.50	1.17	1.14
Percent Reduction for Triclosan vs. Placebo		18.8	26.7	19.3	29.0
p-value		<0.001	<0.001	0.0001	0.0001
Baseline PI	Triclosan	2.14	2.10	2.45	2.45
	Placebo	2.10	2.20	2.43	2.45
6-Month PI	Triclosan	1.33	1.10	1.48	1.63
	Placebo	1.98	1.60	1.68	1.97
Percent Reduction for Triclosan vs. Placebo		32.9	31.3	11.9	17.0
p-value		<0.001	<0.01	0.0001	0.0001

The baseline demographics for the Thai Study, the Swedish Study, and the two pivotal trials are similar for those variables assessed. All of the trials recruited more women than men; the Thai study consists of overwhelming percentage of women. Generally, women are more compliant than men in clinical trials; however, since the gender distribution is equal in placebo and test group, the effect would be controlled. It is well-established that estrogen levels have a great impact on gingivitis; there may be some reason to suspect that different results would be obtained by a predominantly male population - In a pivotal trial, the Agency would likely request a subanalysis by gender. The mean age is comparable in all four groups. The gingival indexes are higher in these two trials than in the U.S. pivotal trials, especially in the Thai Study, although the plaque indexes are somewhat lower. The differences in gingivitis indexes noted after 6 months demonstrate very similar effects to the U.S. pivotal trials. The plaque index shows a much greater difference in the Thai and Swedish studies than the two pivotal trials; however, these numbers are similar to the other non-pivotal trials submitted by the Agency for overseas trials with a baseline prophylaxis. The Agency statistician noted that the standard deviations for the Swedish study is larger than the Thai or the U.S. studies;

however, it was corroborated that the 6-month gingivitis and plaque reductions for both of these studies are comparable to those for the pivotal trials.

In summary, the data from the two trials submitted supports equally efficacious results in subjects who began the trial with or without a professional prophylaxis. The greater percentage of women in the Thai study and the greater baseline GI's and lower baseline PI's for both the Thai and Swedish studies are not ideal for determining generalizability to the U.S. population, but the differences are within limits that allow adequate comparisons for these supporting studies. Nonetheless, the sponsor states that the proposed labelling for TOTAL will indicate initiation of use after a dental hygiene prophylaxis, and that the consumers have professional dental examinations at regular intervals.

Clinically Significant Reductions in Plaque

In response to the original NDA submission, the Agency expressed a concern about an anti-plaque claim due to a lack of evidence for clinical significance of the reductions demonstrated by the pivotal trial data. We asked the sponsor for a definition of clinically significant reduction in plaque. The sponsor replied in this submission that clinically significant reductions of plaque should: 1) meet established criteria for statistically significant difference from placebo controls, 2) demonstrate plaque reductions of at least 10% compared to a placebo control; and 3) "be associated" with reductions of gingivitis which are minimally 15% for each study and 20% for all studies when combined. Although the product meets the above 3 conditions, the rationale for selecting these conditions is not provided, and it is unclear how these conditions are supportive of clinical significance, especially the "10%" value for reduction given in #2.

The literature is inconclusive concerning parameters of plaque reductions that are sufficient to claim clinical significance. Ultimately, the question of clinical significance for the amount of plaque reduction demonstrated in the pivotal studies depends upon the number and duration of health benefits that result. In trying to quantify clinically significant plaque reduction with this product, the sponsor suggests that because gingivitis reduction has been deemed clinically significant in the pivotal trials, plaque must be clinically significant as well; the sponsor sets forth the assumption that the reduction in plaque that is sufficient to produce a significant reduction in gingivitis is by definition clinically relevant. However, the association between plaque and gingivitis, although well-accepted, is not sufficiently defined in terms of amount and type of plaque and the exact amount of contribution to gingivitis that plaque contributes for the agency to accept this argument.

Although plaque is widely-accepted an a contributory factor to periodontal disease, it is not the sole etiologic factor; as was discussed with the sponsor previously, the plaque reduction, in fact, does **not** parallel the gingivitis reduction in magnitude or trend in the two pivotal trials. The sponsor has responded by stating that the lack of parallelness between plaque index

reduction and gingival reduction is not a discrepancy; they state that the reductions of the indices used were not expected to provide absolute consistency across measurements, but do produce statistically significant and directionally consistent across indices and evaluation intervals. While it is a plausible hypothesis that a small reduction in plaque (i.e., 10%) is directly responsible for a clinically significant reduction in gingivitis (20%), this is only speculative as the sponsor has not provided any studies that demonstrate this. It is the onus of the sponsor of the investigational drug to supply documentation and explanation that supports the assertion of clinical relevance.

Although necessary to rule out chance findings, statistical significance provides no evidence about the magnitude of the effect, which is paramount to assessing clinical significance. A very large trial may demonstrate a highly significant reduction (i.e., the probability that this result occurred through chance is enormously small).

The sponsor has also submitted an unpublished paper by Dr. Sebastien Ciancio entitled:

In addition, Dr. Ciancio and three other qualified dentists wrote letters to the NDA in support of the product's ability to decrease plaque and gingivitis in an official submission dated October 31, 1995. Dr. Augusto Elias-Boneta from the University of Puerto Rico's School of Dentistry points out that plaque related diseases are prevalent among the American adult population and more prevalent amongst African and Hispanic Americans. Unfortunately, none of the letters provide evidence towards supporting the claim of significant plaque reduction.

Co-polymer (PVM/MA) anti-plaque effect

One of the trials that the sponsor submitted as pivotal, 90-TRI-0004, tested a placebo that did not contain any co-polymer, whereas all of the other pivotal trials submitted did. The Agency observed that the strength of effect in reducing plaque as measured by a comparison of the plaque index between the test product and the placebo, was significantly greater in this trial than the other pivotal trials. The Agency suggested to the sponsor that the co-polymer may actually be an active ingredient, exerting an anti-plaque effect of its own by "coating" the tooth, or some other means.

Refer to the Tables at the end of this review, which summarize the formulations of the dentifrices and the results of the trials for the following discussion:

Specifically, in Trial 90-TRI-0004, although the formulation of the triclosan test product is not identical to the to-be-marketed (TBM) formulation, the differences between the triclosan test product and the TBM are for all practical purposes, negligible. However, unlike trials 90-TRI-0005 and 90-TRI-0006, the placebo test product in this trial contains no co-polymer. Hence, whereas the two trials that the Agency accepts as pivotal test the effect of triclosan by itself, 90-TRI-0004 is testing the effect of triclosan and the co-polymer combined. If the co-polymer, in fact, exerts an anti-plaque effect of its own, then one would expect a more dramatic improvement in plaque scores when comparing the triclosan dentifrice with co-polymer to the placebo without triclosan or co-polymer. This is in fact, what the results in this trial tend to support - the reduction in plaque index in study 90-TRI-0004 is statistically greater than the reduction seen in either 90-TRI-0005 or 90-TRI-0006. Although attributing this result to the absence of the co-polymer in the placebo dentifrice is speculative at this point, this is the only significant difference between these trials.

The sponsor has responded that the co-polymer is inactive, and has supported this statement with several explanations. The sponsor cautions against making any cross-study comparisons of the absolute magnitude of reductions in plaque or gingival indices. This is a valid point; Although the protocol at all sites is identical, the investigators are different, the population is different- - many factors may contribute to seeing a greater effect in one study over another. Furthermore, although the results do show a greater reduction in plaque indexes in trial 90-TRI-0004, the percent reduction in gingival indexes in this trial lies in between that seen in the other two. Nonetheless, there is a valid reason to question the copolymer's activity.

The sponsor also states that PVM/MA has no antibacterial activity. They state that PVM/MA is present in the formulation to enhance retention and delivery of triclosan to the oral tissues, thereby promoting triclosan's antimicrobial effect, but not acting synergistically. They submitted a study (Attachment 7:V.1 Nabi, Mukerjee et al, *In vitro and in vivo studies on triclosan/PVM/MA copolymer/NaF combination as an antiplaque agent*) in which the in vitro Minimum Inhibitory Concentration (MIC) of triclosan is identical with or without co-polymer. Ideally, another group should have contained co-polymer alone, but the Agency is not claiming that the co-polymer has an anti-bacterial properties. A more plausible description of any activity that co-polymer may possess is the coating action of the co-polymer to prevent attachment of plaque to the dentition.

More compelling evidence submitted by the sponsor is a six-month published study which resulted in no difference in mean plaque indexes between one group of beagles which was exposed to the copolymer, and the other group which received water. The results of the study (Attachment 7- V.2, Gaffar et al, *Longterm Antiplaque, Anticalculus, and Antigingivitis Effects of Benzethonium/Polymer Complex in Beagle Dogs*) shows no difference in plaque indexes between these groups. Although the beagles are considered fairly good models for human periodontal disease, little weight can be given to an animal trial.

Another study was submitted by the sponsor to the NDA in support of the inactivity of the co-

polymer, Gantrez (Attachment 9: Furuichi, Ramberg and Lindhe: *Clinical Study with Placebo, Gantrez Placebo, and Gantrez/Triclosan*). This double-blind, randomized crossover study of 10 subjects evaluated the ability of six test solutions (2 concentrations of Gantrez, 3 different strengths of triclosan with Gantrez, and chlorhexidine) to retard new plaque formation. Each subject received a professional tooth cleaning, and was asked to forego all mechanical plaque control measures for four consecutive days. The subjects rinsed twice daily with 10 ml of the coded mouthwash for 60 seconds. The Plaque Index was scored on day 4, after which a professional tooth cleaning was performed, and after a ten day washout period, the procedure was repeated until each subject used all 6 test solutions and the placebo. The results are tabled as follows:

mouthrinse	mean PI (s.d.)
placebo	0.90 (0.23)
1.984% Gantrez	0.87 (0.10)
1.92% Gantrez	0.85 (0.15)
0.03% triclosan with 1.92% Gantrez	0.83 (0.22)
0.045% triclosan with 1.92% Gantrez	0.78 (0.20)
0.06% triclosan with 1.92% Gantrez	0.72 (0.17)
0.12% chlorhexidine	0.33 (0.17)

The author's conclusion is that there were no significant differences in the mean PI scores between the placebo and the mouthrinses containing Gantrez. Although this is true, it also appears that there is no significant difference between the group of subjects using 0.3 triclosan with Gantrez and the group using Gantrez alone. The numbers are small in this study and any statements about the effect of Gantrez alone on plaque from this limited trial are inconclusive.

The sponsor also submitted a Federal Register notice (Vol 60, No. 31, February 15, 1995) concerning comments on the use of glycerin in OTC topical otic drug products for the prevention of Swimmer's Ear. The statement of relevance to this discussion is, "However, if glycerin functions only as a vehicle (and the need for it as a vehicle is shown) and no claims are made for it as an active ingredient, additional testing would not be required for this ingredient." This statement accepts the premise that glycerine functions only as a vehicle, i.e., without therapeutic activity of its own; this is the very point that the Agency questions.

The sponsor has stated that although they do not feel that additional clinical trials should be required for approval of this NDA, they are willing to commit to the conduct of a phase 4 clinical trial to further characterize the rententivity contributions of the copolymer in the

product.

Conclusions

The sponsor has submitted new data in this NDA amendment in an attempt to correct the deficiencies cited by FDA which prohibited the drug's approval based on the contents of the original NDA. The conclusions of this review are as follows:

1. The sponsor has successfully demonstrated that fluoride's anti-caries effect is maintained when combined with triclosan.

2. OTC status is acceptable because
   a) the product has been shown to be effective without a baseline professional dental scaling and cleaning,
   b) a panel of experts has judged gingivitis an acceptable OTC claim, and
   c) the sponsor has proposed acceptable labelling that is consistent with its limited pediatric indications.

3. The nature of the co-polymer's activity is still inconclusive, but the sponsor has agreed to Phase 4 studies that are properly designed to demonstrate that it is not an active component of the dentifrice.

4. The anti-plaque activity of the dentifrice has not been adequately demonstrated as having a clinically significant effect. Although the dentifrice has been consistently shown to reduce the amount of plaque, the reduction is less than 20%. The sponsor has not demonstrated that the amount of reduction demonstrated has an impact on the health outcome, gingivitis.

Labeling:

The sponsor is proposing this product for over-the-counter use. The sponsor submitted text for carton and tube labeling. No package insert has been proposed by the sponsor.

Several issues that were addressed in the NDA submission must be adequately reflected in the labelling. These are:

1. Clinically significant reductions in plaque were not clinically demonstrated. References to plaque reduction or prevention must be removed.

2. The statement from the American Dental Association's Council on Dental Therapeutics that appears on the tube of the dentifrice asserts the efficacy of the dentifrice in preventing the formation of plaque, a claim that the Agency has not accepted. Use of the American Dental Association's seal and its accompanying statement are considered advertising and cannot

appear on the carton or tube.

3. Although safe use of the product in individuals under 18 has been demonstrated, evidence supporting an effect of the test dentifrice on children for plaque/gingivitis has not been submitted.

4. Levels of gingivitis did not achieve a significant reduction until after 6 months of continuous use of the product.

5. Although supporting studies demonstrated effective gingivitis prevention without a baseline professional prophylaxis, the two pivotal studies enrolled only subjects who received a prophylaxis at baseline. The proposed labelling for TOTAL should indicate initiation of use after a dental hygiene prophylaxis, and that the consumers have professional dental examinations at regular intervals.

6. Clinical trial submitted for demonstration of calculus reduction is deficient. No therapeutic claim for calculus reduction may be made. All calculus claims must be strictly cosmetic.

7. The name TOTAL may be unsuitable for this product. The CDER Labeling and Nomenclature Committee reviewed the proposed name and decided that it is misleading as defined in 21CFR 201.10 (c) (3) since it implies the drug product has some unique effectiveness. (See Appendix 8 of the original NDA review, Consult #200, dated 3/3/93). The sponsor claims that the name is meant to suggest only that use of the dentifrice is part of a total program of oral hygiene, which includes professional care, as well as use of other oral home care products.

8. As per Tentative Final Monograph; Anticaries Drug Products for Over-the-Counter Human Use; 21 CFR Part 355.50: Labeling of anticaries drug products:

(c) Warning. The labeling of the product contains the following warning under the heading "Warning": (1) For all fluoride dentifrice (toothpastes and tooth powders)products. "Keep out of the reach of children under 6 years of age."

(d)Directions. The labeling of the product contains the following statements under the heading "Directions":

(1) – (i) For dentifrices in a paste dosage form with a theoretical total fluorine concentration of 850 to 1,150 ppm identified in §355.10(a)(1), (b)(1), and (c)(1). Adults and children 2 years of age and older: brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor. Instruct children under 6 years of age in good brushing and rinsing habits (to minimize swallowing). Supervise as necessary until capable of using without supervision. Children under 2 years of age: Consult a dentist or doctor."

6 pages

PURGED

(DRAFT LABELING)

Tables

Attachment 1
Dentifrice Formulations Used in the Clinical Trials Submitted (by %)

Protocol Number	90-TRI-0005		90-TRI-0006		90-DP-3-01		89-DP-3-04		90-TRI-004	
	Triclosan Dentifrice	Placebo Dentifrice	Triclosan Dentifrice	Placebo Dentifrice	Triclosan Dentifrice	Placebo Dentifrice	Triclosan Dentifrice	Placebo Dentifrice	Triclosan Dentifrice	Placebo Dentifrice
Triclosan	0.300	0.000	0.300	0.000	0.300	0.000	0.300	0.000	0.300	0.000
Sodium Fluoride	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243	0.243
Deionized Water										
Glycerine USP										
Glycerine										
Dental Type Silica NF										
Silica										
Silica										
Silica										
Non-crystallizing Sorbitol										
Sorbitol										
Poly (Methyl vinyl Ether/Maleic Acid										
Sodium Lauryl Sulfate										
Flavor										
Sodium Hydroxide FCC										
Sodium Hydroxide										
Propylene Glycol USP										
Propylene Glycol										
Titanium Dioxide USP										
Titanium Dioxide										
Iota Carrageenan										
Carrageenan FCC										
Sodium Saccharin USP										
Sodium Saccharin										
Total										

Attachment 2:
Summary of Results for Protocol 90-TRI-0006

		Baseline			3-months			Percent Reduction for Triclosan vs. Placebo	p-value	6-months			Percent Reduction for Triclosan vs. Placebo	p-value
		N	Mean	STD	N	Mean	STD			N	Mean	STD		
Mean Loe/Silness Gingival Index	Triclosan	155	1.4094	0.2163	155	0.9988	0.2847	16.5%	0.0001	154	0.8119	0.2343	29.0%	0.0001
	Placebo	155	1.4287	0.2247	155	1.1880	0.2756			152	1.1441	0.2523		
Mean Gingival Severity Index	Triclosan	155	0.4294	0.1906	155	0.2406	0.1510	25.4%	0.0001	154	0.1454	0.1046	47.6%	0.0001
	Placebo	155	0.4451	0.1948	155	0.3224	0.1457			152	0.2776	0.1346		
Mean Quigley/Hein Plaque Index	Triclosan	155	2.4524	0.4856	155	1.5261	0.5654	4.2%	0.1598	154	1.6341	0.5751	17.0%	0.0001
	Placebo	155	2.4506	0.5009	155	1.5937	0.5105			152	1.9687	0.5296		
Plaque Severity Index	Triclosan	155	0.3373	0.1301	155	0.1906	0.1225	12.5%	0.0455	154	0.1734	0.1135	18.6%	0.0023
	Placebo	155	0.3463	0.1403	155	0.2177	0.1234			152	0.2130	0.1192		

Attachment 3:
Summary of Results for Protocol 90-TRI-0005

		Baseline			3-months			Percent Reduction for Triclosan vs. Placebo	p-value	6-months			Percent Reduction for Triclosan vs. Placebo	p-value
		N	Mean	STD	N	Mean	STD			N	Mean	STD		
Mean Loe/Silness Gingival Index	Triclosan	150	1.2891	0.1803	150	0.9457	0.1990	16.5%	0.0001	145	0.9410	0.1332	19.3%	0.0001
	Placebo	150	1.2952	0.1619	150	1.1327	0.1769			149	1.1656	0.1453		
Mean Gingival Severity Index	Triclosan	150	0.2935	0.1769	150	0.0734	0.1106	55.5%	0.0001	145	0.0474	0.0648	73.3%	0.0001
	Placebo	150	0.2976	0.1579	150	0.1649	0.1479			149	0.1777	0.1357		
Mean Quigley/Hein Plaque Index	Triclosan	150	2.4532	0.3824	150	1.6523	0.4287	6.7%	0.0012	145	1.4800	0.4864	11.9%	0.0001
	Placebo	150	2.4334	0.3448	150	1.7711	0.4153			149	1.6799	0.4478		
Plaque Severity Index	Triclosan	150	0.2531	0.1444	150	0.0898	0.0847	20.3%	0.0034	145	0.0935	0.0885	18.7%	0.0110
	Placebo	150	0.2433	0.1359	150	0.1126	0.0992			149	0.1150	0.0997		

Attachment 4:
Summary of Results for Protocol 90-TRI-0004

		Baseline			3-months			Percent Reduction for Triclosan vs. Placebo	p-value	6-months			Percent Reduction for Triclosan vs. Placebo	p-value
		N	Mean	STD	N	Mean	STD			N	Mean	STD		
Mean Loe/Silness Gingival Index	Triclosan	60	1.1703	0.1920	60	1.2878	0.2550	19.3%	0.0001	58	0.8740	0.2061	26.5%	0.0001
	Placebo	64	1.1569	0.1761	64	1.5178	0.3603			63	1.1887	0.2696		
Mean Gingival Severity Index	Triclosan	60	0.2628	0.1580	60	0.3726	0.1937	31.9%	0.0001	58	0.1194	0.0798	57.9%	0.0001
	Placebo	64	0.2367	0.1363	64	0.5471	0.2113			63	0.2838	0.2037		
Mean Quigley/Hein Plaque Index	Triclosan	60	1.7700	0.3389	60	1.3345	0.3861	20.1%	0.0001	58	1.1062	0.3437	32.2%	0.0001
	Placebo	64	1.7517	0.3553	64	1.6698	0.5112			63	1.6321	0.3936		
Plaque Severity Index	Triclosan	60	0.2070	0.1340	60	0.1080	0.1044	50.4%	0.0001	58	0.0453	0.0593	75.7%	0.0001
	Placebo	64	0.1933	0.1337	64	0.2054	0.1655			63	0.1864	0.1151		

Dental Officer's Review of NDA 20-231

SEP 8 1994

Original Amendment

Drug: Triclosan 0.30%, sodium fluoride USP 0.24% dentifrice (Colgate Total™ Toothpaste)

Sponsor: Colgate-Palmolive Company

Submission date: May 3, 1994
Received date: May 4, 1994
Review date: August 29, 1994

CSO: Santford Williams

Proposed indication:
Prevention of plaque, caries and gingivitis

Pharmacologic Category:
Anti-caries, anti-plaque, anti-gingivitis agent

Background:

A review for this NDA has been written, and is currently circulating through the center for final action. This unsolicited submission from the sponsor contains the four-month safety update report for Colgate Total Toothpaste and a revised request for a period of marketing exclusivity.

Marketing Exclusivity

Revision:

In the original NDA submission, a period of 5 years exclusivity was requested by the sponsor. Following are the criteria that the sponsor used to make the determination in the original submission:

1. Approval for this product will be after September 24, 1984

2. This product contains a new chemical entity, triclosan, as defined by the Food and Drug Administration. That is, no product containing triclosan has been approved by the Agency previously;

3. The pivotal plaque and gingivitis clinical investigation studies submitted in the clinical data section of this submission, namely the five main studies submitted in Item 8.D(1), are essential to approval;

4. The studies in NDA Item 8.D(1), referenced above , represent new clinical investigations as set forth in proposed §314.108(a); and

5. The studies in NDA Item 8.D(1), referenced above, were conducted or sponsored by the applicant under the investigational new drug application for this product, IND

The new submission replaces the following language for #2 above; all of the other points remain unchanged.

2. This product contains triclosan which is the subject of an approved NDA. This is Colgate-Palmolive NDA 16-486, for P-300 Antibacterial Soap. This NDA was submitted to FDA on September 1, 1966 and was approved January 24, 1969. It is currently inactive as the product is not being marketed.

Discussion:

The sponsor was incorrect in requesting 5-year exclusivity in the original submission . As was reported in the *Background* section of the clinical review for the original NDA, a triclosan-containing antibacterial soap was approved in 1969 through the NDA process. In order for the dentifrice to meet the requirements for 5-year exclusivity, it would have to be a new moiety. Since it is not, according to FDA regulations, a three-year exclusivity will be applied if the application contains "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." An investigation is "essential" if the Agency could not have approved the application or supplement without relying on that investigation. To be considered "new", the investigation has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product. The current NDA submission meets all of the criteria for three-year exclusivity. If approved, a three-year exclusivity will apply.

Adverse Events:

Reporting:

Since the NDA was filed, the sponsor reports not having obtained any new data through preclinical or clinical studies which would negatively affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. There was one report received from Canada, where Total dentifrice is marketed, of one alleged sensitivity reaction.

The sponsor stated that subsequent patch testing of the subject was positive for the product.

Discussion:

There were no reports in the original NDA submission of sensitivity to the product with confirmed patch testing. However, in the original submission, there was a section on adverse reactions reported by consumers in countries where the product is currently in use. This did include one report of sensitivity to the dentifrice in Great Britain confirmed by patch testing. It would be helpful if the results of the patch test provided information on whether the sensitivity was to the triclosan component of the dentifrice, or one of the other ingredients. This new information does not alter the recommendations regarding approval of the dentifrice.

Frederick Hyman

Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA Amendment
HFD160/Div File
HFD-160/DO/Hyman
HFD-160/CSO/Williams

Dental Officer's Review of NDA 20-231
Addendum to NDA Review

Drug:	Triclosan 0.30%, sodium fluoride USP 0.24% dentifrice (Colgate Total™ Toothpaste)	**Serial Number:**	NAZ
		Submission date:	July 31, 1995
		Received date:	July 31, 1995
		Review date:	January 17, 1996
Sponsor:	Colgate-Palmolive Company	**CSO:**	Roy Blay

Proposed indication:
Prevention of plaque, caries and gingivitis

Pharmacologic Category:
Anti-caries, anti-plaque, anti-gingivitis agent

Summary

This addendum reflects additional comments to the original review of this NDA amendment, dated September 12, 1995, which have resulted from discussion within the Office of Drug Evaluation V since the initial review was completed. The sponsor will be sent an approvable letter, but final approval will be withheld until resolution of plaque and pediatric labelling issues. The Dental Products Panel OTC Plaque Products Subcommittee will meet on February 29, 1996 to discuss and reach a consensus on two issues: 1) whether the lack of data on gingivitis data on children can be sufficiently communicated through labelling, or whether stronger action, such as prescription status is necessary to prevent its use in children; and 2) the level of plaque reduction between placebo and test product that is necessary to claim anti-plaque activity.

Background

An NDA for this product was reviewed by the Division of Medical Imaging, Surgical, and Dental Drug Products (HFD-160) and resulted in a "not approvable" action of which the sponsor was motified on January 25, 1995. On July 31, 1995, the sponsor submitted an amendment to the original NDA, consisting of several volumes which include a revised point-by-point rebuttal of the Agency's non-approval issues, new study data, publications, and discussion. In the original review of this amendment, dated September 12, 1995, recommendation was made for approval of the NDA with the following caveats:

Additional correspondence, meetings and phone conversations that have occurred since the original review of the NDA resubmission have prompted discussion about the level of clinically significant anti-plaque activity that would allow an anti-plaque designation for this dentifrice, as well as the appropriateness of pediatric labelling.

Discussion:

Anti-Plaque

Unlike gingivitis, plaque, by itself, is not a health outcome. During past meetings, the Dental Products Panel OTC Plaque Products Subcommittee has reached a consensus that plaque and gingivitis claims should be considered together. Published literature, including an article by a task force of experts gathered by the American Dental Association's (ADA) Council on Dental Therapeutics, supports demonstration of a 20% difference in subjects' average gingival indexes between an active control group and a test group for that product to receive an ADA anti-gingivitis seal. On the other hand, no published literature has been uncovered that supplies guidelines for a plaque claim.

Without plaque guidelines, the conclusion presented in the prior review was that a 20% reduction should also be demonstrated for the associated plaque claim, which clinical trials submitted to this NDA do not achieve; in fact, the plaque reduction, does not parallel the gingivitis reduction in magnitude or trend in the two pivotal trials. Although plaque is widely-accepted as a contributory factor to periodontal disease, the exact relationship is unknown. The sponsor has responded by stating that the lack of parallelness between plaque index reduction and gingival reduction is not a discrepancy; they state that the reductions of the indices used were not expected to provide absolute consistency across measurements, but do produce statistically significant and directionally consistent across indices and evaluation intervals. While it is a plausible hypothesis that a small reduction in plaque (i.e., 10%) is directly responsible for a clinically significant reduction in gingivitis (20%), this is only speculative as the sponsor has not provided any studies that demonstrate this. The sponsor has not provided compelling evidence that this is the case in their trials.

Many products on the market, however, are allowed to make anti-plaque and anti-gingivitis claims currently and may continue to do so during the time that the panel will be weighing the evidence to develop a monograph. The sponsor has met with members of the NDA review and compliance staff to voice displeasure with perceived unfair treatment regarding the NDA process for an anti-plaque/anti-gingivitis claim vs. products making claims under the monograph review process. In addition, anti-plaque claims by themselves are allowed on the labels of dentifrices that meet the OTC monograph for anti-caries products. There is concern within the Agency regarding the nature of the claims that some of the monographed products are making and the Agency is sympathetic to the sponsor's intensive NDA process.

Pediatric Efficacy

The sponsor demonstrated efficacy of the product in children for caries reduction that is equivalent to marketed fluoride dentifrices. The 3-year trial that was completed enrolled approximately 4,000 children, ages 11 - 15, and also resulted in no adverse events that were related to use of the dentifrice. However, none of the pivotal trials studying plaque/gingivitis enrolled individuals under the age of 18. The sponsor's draft labelling clearly states that the efficacy of the dentifrice has not been established in individuals under the age of 18. However, the Agency is concerned that this language may be largely ignored by the public, and the product will be used extensively in children as well as adults if allowed to be marketed OTC. Without demonstration of anti-gingivitis efficacy in children, there is no advantage to the use of this product over currently accepted anti-caries dentifrices.

Other Issues

Procter and Gamble has formally submitted results of trials that they have conducted with Colgate's triclosan/fluoride dentifrice (IND rial 027, submission date 10/6/95). They stated that they were unable to replicate the results in trials with the same investigator as Colgate. They felt that one of their problems was being unable to recruit subjects with baseline gingivitis scores that were as high as Colgate's. They then went on to state that their analysis suggested that the subjects recruited in Colgate's published trials had baseline gingivitis scores that were greater than 90% of individuals in this country. Their conclusion was that this testing did not support an OTC claim for a triclosan/fluoride dentifrice.

The Agency discussed these findings, and decided that the lack of positive findings by one sponsor does not negate the results of several pivotal trials formally submitted by the sponsor to the NDA. Although we have been unable to explain the discrepancy, it is difficult to account for minor changes in protocol as would be the case in trials conducted by two different sponsors. In terms of the subjects chosen being representative of individuals in this country with gingivitis, the Agency re-analyzed the results for an effect from baseline gingivitis score. The statistician found similar results at all levels of entering gingivitis scores. As a result, although it is disconcerting that Procter and Gamble was unable to reproduce the findings of Colgate, the sponsor's results hold up under scrutiny as being valid, and efficacious in individuals with rather mild levels of gingivitis, which echoes the current U.S. population.

Conclusions:

It is felt that the pediatric and plaque labelling issues are controversial enough that more input from experts is warranted in this area. It has been arranged that on February 29, 1996, the Dental Products Panel OTC Plaque Products Subcommittee will discuss these issues to provide advice to the Agency.

Regulatory Action:

An approvable letter will be sent to the sponsor for this NDA resubmission. In light of the new developments regarding this NDA as outlined in this review, provisions are being placed on this product's approval in addition to the phase 4 recommendations that the Agency decided to include to conclusively establish the activity of the co-polymer. During the next meting of the Plaque Subcommittee of the Dental Products Panel, which is scheduled for February 29, 1996, the panel will discuss both the pediatric indications for the dentifrice and a definition of clinically significant plaque reduction in conjunction with gingivitis. The sponsor will be advised that the exact labelling will not be agreed upon until after a consensus on these two issues is reached by the Panel.

Frederick Hyman

Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA
HFD-550/Div File
HFD-550/DO/Hyman
HFD-550/CSO/Blay

1/18/96

Dental Officer's Review of NDA 20-231
NDA Review

MAY 30 1997

Drug:	Triclosan 0.30%, sodium fluoride USP 0.24% dentifrice (Colgate Total™ Toothpaste)	**Serial Number:**	AZ
		Submission date:	January 13, 1997
		Received date:	January 14, 1997
		Review date:	May 12, 1997
Sponsor:	Colgate-Palmolive Company	**PM:**	Harold Blatt
Proposed indication:	Prevention of plaque, caries and gingivitis	**Pharmacologic Category:**	Anti-caries, anti-plaque, anti-gingivitis agent

Background

An NDA for this product was reviewed by the Division of Medical Imaging, Surgical, and Dental Drug Products (HFD-160) and resulted in a "not approvable" action of which the sponsor was notified on January 25, 1995. On July 31, 1995, the sponsor submitted an amendment to the original NDA, consisting of several volumes which included a revised point-by-point rebuttal of the Agency's non-approval issues, new study data, publications, and discussion. On January 31, 1996, the agency issued a letter, in which the product was deemed "approvable" with regard to anti-caries and anti-gingivitis claims. In the letter, it was also acknowledged that the final carcinogenicity study was still under review. The sponsor submitted new data on March 7, 1996 and received an approvable letter of September 5, 1996 in which the sponsor was required to demonstrate that use of Total toothpaste would not result The current submission is in response to that approvable letter.

The current NDA resubmission addresses the two options that were presented in the September 5, 1996 approvable letter to clarify the safety issue:

On January 30, 1997, a meeting took place between the sponsor and the agency in which the reasons for the action letter were discussed

After several discussions between the sponsor and the Agency regarding design of an acceptable pharmacokinetic protocol, the study was initiated and the results will be submitted to the Agency during this

review period. [1]

A labeling meeting was held in June, 1996, prior to the development of pending safety issue, between representatives of all involved review disciplines, including the Division of Dermatologic and Dental Drug Products, Over-the-Counter Drug Products, Chemistry, Pharmacology, and Statistics. At the conclusion of the meeting, a draft label was accepted pending two unresolved issues: 1) wording of the anti-plaque claim, and 2) use of the phrase "long-lasting antibacterial." In anticipation of the drug's possible approval during the current review period, a labeling meeting has been scheduled for June 9, 1997 to finalize the labeling of the product. This review will address only the anti-plaque activity of this dentifrice, referencing additional correspondence and meetings since the last review of this NDA about the level of clinically significant anti-plaque activity that would support an anti-plaque claim.

RJ 5/30/97

Summary

Although plaque is widely-accepted as a contributory factor to periodontal disease, the exact relationship is unknown. It is probably the quality of the plaque (i.e., bacterial composition) in addition to the quantity of plaque present that determines the extent of gingivitis that results in any given individual. It is unclear what effect removal of plaque will have on preventing gingivitis; therefore, demonstration of plaque removal alone does not automatically demonstrate a therapeutic endpoint, i.e., reduction in gingivitis. On the other hand, it is well accepted that reduction in existing gingivitis results from removal of its etiologic agent, plaque. If a reduction in gingivitis is demonstrated with concomitant reduction in plaque, it is ~~clear~~ likely that at least part of that therapeutic benefit of gingivitis reduction has been achieved through the reduction of plaque. The Plaque/Gingivitis Subcommittee of the Dental Products Panel has made it clear that the members prefer to approve concomitant gingivitis and plaque claims, as a gingivitis claim without a plaque approval may imply that there is some other mechanism of action other than plaque reduction that is causing the anti-gingivitis effect.

RJ 5/30/97

At the most recent meeting of the Plaque/Gingivitis Subcommittee held on May 8, 1997, Procter & Gamble presented plaque and gingivitis reduction data in support of cetylpyridinium chloride (CPC). The magnitude and consistency of the data sufficiently impressed the panelists, who unanimously voted to approve this ingredient for reduction of both plaque and gingivitis - this is the first product that the panel has approved for both claims. The amount of gingival and plaque index reduction found in CPC trials was nearly identical to the reduction demonstrated in the two pivotal trials submitted by Colgate in the Total NDA. The panel confirmed through its vote that the value of plaque index and gingival index reductions

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[1]Refer to pharmacokinetic reviews and meeting minutes for details on the pharmacokinetic issues; reviews of the labeling comprehension studies by the OTC Division in conjunction with DDMAC for details on the labeling comprehension studies.

exhibited by both CPC and Colgate Total are consistent with meaningful therapeutic claims.

Since the plaque reduction is consistent with gingivitis reduction, occurs concurrently, and may be of sufficient magnitude to have clinical importance, a concomitant anti-plaque/anti-gingivitis claim has been demonstrated. It is recommended that Colgate's triclosan dentifrice be allowed to state both anti-plaque and anti-gingivitis claims on its label.

Discussion:

Unlike gingivitis, plaque, by itself, is not a health outcome. This is supported by both published literature and discussions that have resulted from FDA advisory groups.[2] One article authored by a task force of experts gathered by the American Dental Association's (ADA) Council on Dental Therapeutics, is specific about what is necessary to claim gingivitis reduction. The ADA supports demonstration of a 20% difference in subjects' average gingival indexes between an active control group and a test group for that product to receive its anti-gingivitis seal. However, no such published literature has been uncovered that supplies guidelines for clinically important plaque reduction.

The Plaque Subcommittee of the Dental Products Panel was convened in 1993 with the charge of writing an OTC monograph for products currently on the market that wish to continue marketing with claims of reduction in the formation of plaque/gingivitis. The primary task before the Subcommittee has been to reach a consensus about plaque and gingivitis claims, including their interrelationship and criteria for their acceptance. Early on in the deliberations, the question of plaque being included at all as a drug claim was discussed. Some members of the panel were leaning towards making plaque strictly a cosmetic claim. After presentations and discussion, the panel concluded that unless the statement about plaque was clearly cosmetic (e.g., "helps clean away plaque from teeth and gums giving cleaner, fresher mouth"), it should be regulated under the OTC Drug Monograph. (Meeting June 28-29, 1994). On December 7, 1994, the Subcommittee accepted the following statement: "All references to the control of dental plaque, or its equivalence, with or without qualifications, will be interpreted as a drug claim." Furthermore, most members of the Subcommittee believe that the endpoint of effectiveness studies should be reduction and/or prevention of plaque with concomitant reduction and/or prevention of gingivitis (page 8, notes, December 5-7, 1994 minutes).

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[2] Clark's Clinical Dentistry, 1993, review articles by Kornman, 1986, Land and Brecx, 1986, Addy 1986, Fardel and Turnbull, 1986, Tinanoff 1990 and various references cited clearly establish a lack of consistent causal relationship between plaque and gingivitis. Examples: Vol.3/Chapter 1. Page 6 states "...not all plaque causes disease"; Vol 3/Chapter 12. Page 1 Clark's states: "The pathogenic potential of plaque can vary from one individual to another and from tooth to tooth within an individual."

What is the relationship between plaque and gingivitis?

With rare exceptions, gingivitis is always preceded by chronic exposure to plaque; however, not everyone with plaque develops gingivitis. Therefore, although plaque is widely-accepted as a contributory factor to periodontal disease, the exact relationship is unknown [3]. It is probably the quality of the plaque (i.e., bacterial composition) in addition to the quantity of plaque present that determines the extent of gingivitis that results in any given individual. It is unclear what effect removal of plaque will have on preventing gingivitis; therefore, the panel has reasoned, demonstration of plaque removal alone does not automatically demonstrate a therapeutic endpoint, i.e., reduction in gingivitis. On the other hand, it is well accepted that reduction in existing gingivitis results from removal of its etiologic agent, plaque. If gingivitis reduction is demonstrated with concomitant reduction in plaque, it is ~~clear~~ that at least part of that therapeutic benefit of gingivitis reduction has been achieved through the reduction of plaque.[4] A problem may arise when gingivitis reduction is demonstrated, without a reduction in plaque.

What about stand-alone gingivitis claims?

It has become clear during the evolution of the panel meetings that the Committee is uncomfortable with approving a gingivitis claim without a plaque claim as an OTC product, since the obvious question would remain, i.e., if the reduction in gingivitis formation is not achieved through a concomitant reduction in plaque, what is the mechanism? A discussion on this topic arose at the May 8, 1997 meeting. If the mechanism is anti-inflammatory, i.e., reducing the inflammation of the gingiva (the hallmark of gingivitis) while not reducing the formation of plaque (the etiologic agent for gingivitis), this product may be masking a progression of gingivitis to periodontitis while giving the consumer a false sense of security, the panel reasoned. As such, this type of product would not be appropriate as a product that is available without the oversight of a health professional.

What about stand-alone anti-plaque claims?

It is also becoming clear that the panel will not approve a product that only demonstrates

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[3] Clark's Clinical Dentistry: Vol.2/Chapter 3, page 19 states, "There is no convincing evidence of a linear relationship between the quantity of plaque and the extent of periodontal disease. Rather, the relationship between the amount of plaque and the threshold for disease most likely depends on the specific bacterial composition of the plaque and the resistance of the host."

[4] Kornman continues: "Based upon current knowledge, it seems reasonable to conclude that the prevention of gingivitis requires regular, efficient plaque removal."

plaque reduction without submitting evidence of gingivitis reduction. As discussed above, this is largely due to the panel's belief that reduction in plaque does not automatically result in gingivitis reduction - and without gingivitis reduction, there is no therapeutic benefit. One such example of the panel's feeling about stand-alone plaque claims was evidenced by their evaluation of Microdent™, a dimethicone product that its sponsors claim coats the teeth and mechanically prevents plaque from adhering. The manufacturer of Microdent was asking only for an anti-plaque claim, specifically not requesting approval as an anti-gingivitis agent. In the few studies that monitored gingivitis, no detectable difference was observed between the test as compared to the control groups, according to the panel report. The reviewer in fact commented that although the plaque effect was statistically significant, it is not clinically relevant, and it is misleading to claim that the product has a plaque inhibitory effect, since such a claim might suggest a beneficial therapeutic effect. During the May 8, 1997 meeting, the sponsor of Microdent presented more information about the plaque-reducing abilities of the product, and stated that they do not want to address gingivitis reduction or prevention. The panel again made it clear that plaque could not stand alone as a therapeutic claim, and voted unanimously that the product should be in Category 3 for efficacy, i.e., insufficient information to approve.

What level of gingivitis and plaque reduction is the panel accepting?

On December 17, 1996, data in support of cetylpyridinium chloride (CPC) as an active ingredient in products to prevent plaque and gingivitis were presented by Procter & Gamble (Refer to the table following this paragraph). The data presented can be summarized as follows: The average percent reduction in the gingivitis ranged between 15 and 40%, with reductions in supra gingival plaque ranging between 15 and 28%, all significant at $p < 0.05$. On May 8, 1997, Procter & Gamble returned to present some new analyses of their data. In addition to the percent reductions in mean indexes, they expressed odds ratios (percent of subjects that demonstrated 33% or greater improvement, vs. percent of subjects who showed less than 33% improvement), and percent of sites that improved vs. those that did not improve with each product. The magnitude and consistency of the data sufficiently impressed the panelists, who unanimously voted yes on efficacy for both plaque and gingivitis.

Comparison of indexes reported in CPC Trials and Colgate Total trials (reported as % reduction)

	Pivotal studies				Supporting Studies					
	GI	PI	GI	PI	GI	PI	GI	PI	GI	PI
CPC (4 studies) Study Number	005293		002393		CC-121		CC-125			
% reduction	23.0	17.3	15.7	17.7	28.3	15,2	25.5	18.5		
Colgate TOTAL™ Study Number	90-TRI-0006		90-TRI-0005		90-TRI-0004		89-DP-3-04		90-DP-3-01	
% reduction	29.0	17.0	19.3	11.9	26.5	32.2	31.8	58.0	19.2	25.0

GI = gingival index
PI = plaque index

percent reduction = difference between reduction in index in placebo compared to active

How does this vote affect the approval of the Colgate NDA?

The agency has learned through observing the experts on the subcommittee that it would be beneficial in future trials of anti-plaque/gingivitis agents for the review division to ask individual sponsors of NDA's to present data both as percent reduction as well as odds ratios and percent of sample population that achieved beneficial therapy. However, there is insufficient reason to believe that a reanalysis of the data in this manner would provide new information to support product approval - in fact, gingivitis efficacy has already been approved for this drug without this reanalysis (See approvable letter dated January 31, 1996). **What the reanalysis of the CPC data did confirm was that the value of plaque index and gingival index reductions exhibited by both CPC and Colgate Total are consistent with meaningful therapeutic claims.**

Conclusions:

In summary, after reviewing the data from clinical trials conducted for CPC, the panel voted unanimously to approve this ingredient for reduction of plaque and reduction of gingivitis. The amount of gingival and plaque index reduction found in CPC trials was nearly identical to the reduction in the pivotal trials submitted by Colgate in the Total NDA. The panel has made

it clear that the members prefer to approve concomitant gingivitis and plaque claims, as a gingivitis claim without a plaque approval may imply that there is some mechanism of action other than plaque reduction that is causing the anti-gingivitis effect. Since the plaque reduction is consistent with gingivitis reduction, occurs concurrently, and is of sufficient magnitude for the panel to have clinical importance, a concomitant anti-plaque/anti-gingivitis claim has been demonstrated.

Regulatory Action:

It is recommended that Colgate's triclosan dentifrice be allowed to state both anti-plaque and anti-gingivitis claims on its label.

Fred Hyman

Frederick N. Hyman, D.D.S., M.P.H.

APPEARS THIS WAY ON ORIGINAL

cc: Orig NDA
HFD-540/Div File
HFD-540/DD/Wilkin
HFD-540/TL/Kelsey [signature] 5/21/97
HFD-540/DO/Hyman/Gilkes
HFD-540/PM/Blatt
HFD-540/See
HFD725/Srinivasan
HFD-/830/Vidra

claims in prevention of plaque (surrogate) and gingivitis to be allowed w/ SOI => antigingivitis, as well as [illegible] fluoride [signature] 01/09/97

[signature] 5/30/97 As above, with notes in the text and the following comments:

1. Throughout the review there are statements such as the Plaque / Gingivitis Subcommittee of the Dental Products Panel would "approve" particular claims. Such statements are regarded as elliptical grammatical constructions, since the Subcommittee's conclusions are advisory to the Agency and not otherwise binding. The Subcommittee may <u>recommend</u> approval.

2. Proof of causality must be distinguished from the regulatory basis for approval;

a. The demonstration of plaque reduction, either alone or in the presence of gingivitis reduction, does <u>not</u> establish a <u>sufficient</u> causal relationship. Thus, plaque reduction <u>alone</u> cannot provide the basis for approval of gingivitis claims.

b. The demonstration of gingivitis reduction in the absence of the demonstration of plaque reduction allows for a possible mechanism that masks the signs of gingivitis while progression to periodontitis continues. Thus, the demonstration of plaque reduction is <u>necessary</u> <u>but</u> <u>not</u> <u>sufficient</u> for approval of gingivitis claims.

c. The demonstration of BOTH plaque reduction AND gingivitis reduction is <u>necessary and</u> <u>sufficient</u> for approval of (OVER)

gingivitis claims. The demonstration of EITHER plaque reduction OR gingivitis reduction but NOT BOTH is insufficient for approval of gingivitis claims for OTC products.

d. Even though plaque reduction per se is not a clinically meaningful outcome, it is still necessary (although not sufficient) for approval of gingivitis claims for OTC product Products for which the sponsor has demonstrated BOTH plaque reduction AND gingivitis reduction should have in the product labeling both anti-plaque and anti-gingivitis claims since demonstration of BOTH is necessary for an OTC product.

APPEARS THIS WAY ON ORIGINAL

e. The apparent asymmetry within the regulatory value of the demonstration of plaque reduction is that plaque reduction by itself is NOT a surrogate for gingivitis reduction, but plaque reduction in the presence of gingivi reduction is, in general, sufficient to rule out alternative mechanisms of gingivitis reduction. The validation of a surrogate (described elsewhere) has not been established for plaque reduction as a surrogate for gingivitis reduction.

However, in the presence of demonstrated gingivitis reducti the demonstration of plaque reduction would require for a drug product to have a masking effect on the signs of gingivitis permitting progression to periodontitis that BOTH (a) plaque reduction is insufficient in the treatment AND (b. the drug product has a SECOND biologically significant effe

Although such a concurrence of features cannot be excluded by formal deductive logic, the CRITERION OF SIMPLIC employed in inductive logic provides for the finding that such concurrence is unlikely, complicated, and, in general, insufficiently compelling, in the absence of additional evidence to direct the sponsor to conduct additional studies.

MEDICAL OFFICER LABELING REVIEW
Division of Over-The-Counter Drug Products

NDA: 20-231
NAME: Colgate Total™ Toothpaste (triclosan 0.30%, sodium fluoride USP 0.24% dentifrice)
SPONSOR: Colgate-Palmolive Company
P.O. Box 1343
909 River Road
Piscataway, NJ 08855-1343
TYPE OF SUBMISSION: Commercial Pharmaceutical Draft Product Labeling
DATE OF SUBMISSION: January 13, 1997 **CDER:** January 14, 1997
DATE OF REVIEW: April 8, 1997
REVIEWER: Rosemarie Neuner, MD, MPH
CSO: Ms. Stephanie Mason

Background

Colgate Total™ Toothpaste is a dentifrice containing the active ingredients triclosan 0.30% and sodium fluoride USP 0.24%, that has been developed for the over-the-counter market by the Colgate-Palmolive Company. The sponsor is seeking approval for the following proposed indications: the reduction and prevention of dental plaque, gingivitis and dental caries. Triclosan is a broad-spectrum, topical antimicrobial agent that is used in soaps and other marketed topical disinfectant products. On January 31, 1996, the agency issued an approvable letter to the sponsor for the indications of anticaries and antigingivitis and requested the sponsor to submit additional information in support of their antiplaque claim. A regulatory decision regarding an antiplaque indication for this dentifrice is still pending. A second approvable letter to the sponsor was issued on September 5, 1996 due to agency concerns regarding the potentia

These issues are of particular concern in children. In the September 1996 approvable letter, the agency requested that the sponsor

In response to the agency's request, the sponsor did two types of comprehension studies: conventional label comprehension studies and simulated shelf purchase studies. This review is of final draft product label submitted to the agency by the sponsor on January 13, 1997 derived from data generated from the results of these four consumer use trials. The consumer use comprehension trials have been reviewed and discussed as a separate issue from the proposed product labeling for this product by both the Division of Drug Marketing and Advertising Communications (HFD-40) and by this reviewing division (HFD-560). (Refer to the comments in the memo from HFD-40

to the Colgate Total™ Toothpaste NDA file 20-231 dated 3/21/97 for the former, and the medical officer study review dated 4/8/97 by Rosemarie Neuner, MD, for the latter.)

Proposed Draft Labeling

a. End Flaps -

2 PAGES PURGED

(DRAFT LABELING)

General Comments:

10. The sponsor may want to redo this labeling so that it is in compliance with the February 27, 197 printed monograph on Proposed Labeling Requirements for OTC Drug Products.

11. Attached is a prototype fluoride toothpaste label that the sponsor may want to use as reference. (See attached figure, Fig. 7.)

Rosemarie Neuner, MD

Rosemarie Neuner, MD, MPH
Medical Officer, HFD-560

Linda M. Katz, MD, MPH 7/9/97
Deputy Director, HFD-560

Attachments: Figures 1-7.
cc: orig NDA
HFD-560/Div. File
HFD-560/IDS/Sherman
HFD-560/MO/Neuner
HFD-560/Dep Dir/Katz
HFD-560/Div Dir/Bowen
HFD-540/Div. File
HFD-540/DO/Hyman
HFD-540/Dent Team Leader/Kelsey

As above except that "plaque" and may be included in the list of indications.

6/24/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

CHEMISTRY REVIEW(S)

Division of Medical Imaging, Surgical and Dental Drug Products

Review of Chemistry, Manufacturing, and Controls

OCT 13 1995

NDA #: 20-231 **CHEM.REVIEW #:** 3 **REVIEWER:** P.Stewart

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-29-92	12-30-92	2-07-93
AMENDMENT	9-29-93	9-30-93	12-01-93
Filing Date	12/24/93		
Amendment	3/13/95	3/14/95	3/20/95
New Correspondence	5/30/95	6/2/95	6/19/95
Amendment	7/31/95	7/31/95	8/2/95

NAME & ADDRESS OF APPLICANT: Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08855-1343

DRUG PRODUCT NAME

Proprietary: Colgate Total Toothpaste

Nonproprietary/USAN: Triclosan 0.30%, Sodium Fluoride USP 0.24%

Chem.Type/Ther.Class: 4 S

PHARMACOL.CATEGORY/INDICATION: Anti-plaque, anti-gingivitis, anti-caries

DOSAGE FORM: Dentifrice

STRENGTHS: Triclosan 0.3%, NaF 0.24%

ROUTE OF ADMINISTRATION: Topical to the teeth followed by expectoration

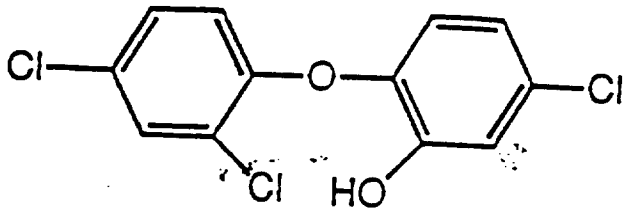
DISPENSED: ___ Rx _X_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: 2,2,4'-trichloro-2'-hydroxydiphenyl ether

Molecular Formula: $C_{12}H_7Cl_3O_2$

Molecular Weight: 289.6



Triclosan

SUPPORTING DOCUMENTS:

CONSULTS:

Environmental Assessment - acceptable 12/8/93
Labeling Committee - "Total" not appropriate in name.
Establishment Evaluation - Acceptable 6/16/94

This submission seeks FDA approval for Colgate Total (sodium fluoride USP 0.24%, triclosan 0.30%) Toothpaste in the United States with triclosan as the antiplaque and antigingivitis active ingredient. The FDA Labeling Committee did not approve of "Total" in the name. Proposed expiration 24 months.

CONCLUSIONS & RECOMMENDATIONS:

Colgate's response to the Labeling Committee's comments on the tradename "Colgate Total Toothpaste" was sent back to the Labeling Committee for further review. The comments from the chemist who reviewed the Methods Validation Package should be forwarded to Colgate

Patricia Stewart
Review Chemist, HFD-160
September 29, 1995

10-13-95

cc:
Orig. NDA 20-231
HFD-160/Division File
HFD-160/DivDir/Love
HFD-160/Chem/Stewart
HFD-160/Dental/Hyman
HFD-160/Pharm/Bailey
HFD-160/Micro/Vincent
HFD-160/CSO/Santford Williams

Division of Medical Imaging, Surgical and Dental Drug Products

Review of Chemistry, Manufacturing, and Controls

JUL - 6 1995

NDA #: 20-231 CHEM.REVIEW #: 2 REVIEWER: P.Stewart

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-29-92	12-30-92	2-07-93
AMENDMENT	9-29-93	9-30-93	12-01-93
Filing Date	12/24/93		
Amendment	3/13/95	3/14/95	3/20/95
New Correspondence	5/30/95	6/2/95	6/19/95

NAME & ADDRESS OF APPLICANT: Colgate-Palmolive Company
909 River Road
Piscataway, NJ 08855-1343

DRUG PRODUCT NAME

Proprietary: Colgate Total Toothpaste

Nonproprietary/USAN: Triclosan 0.30%, Sodium Fluoride USP 0.24%

Chem.Type/Ther.Class: 4 S

PHARMACOL.CATEGORY/INDICATION: Anti-plaque, anti-gingivitis, anti-caries

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ROUTE OF ADMINISTRATION: Topical to the teeth followed by expectoration

DISPENSED: ___ Rx _X_ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: 2,2,4'-trichloro-2'-hydroxydiphenyl ether

Molecular Formula: $C_{12}H_7Cl_3O_2$

Molecular Weight: 289.6

SUPPORTING DOCUMENTS:

CONSULTS:

Environmental Assessment - acceptable 12/8/93
Labeling Committee - "Total" not appropriate in name.
Establishment Evaluation - Acceptable 6/16/94

REMARKS/COMMENTS:

This submission seeks FDA approval for Colgate Total (sodium fluoride USP 0.24%, triclosan 0.30%) Toothpaste in the United States with triclosan as the antiplaque and antigingivitis active ingredient. The FDA Labeling Committee did not approve of "Total" in the name. Proposed expiration 18 months.

CONCLUSIONS & RECOMMENDATIONS:

Colgate's responses to our comments were satisfactory as far as they went, but each response ended with "data will be provided in Colgate's complete response". We will have to wait for the "complete response" before a final decision is made on the adequacy of the NDA.

Patricia Stewart 6/30/95
Review Chemist, HFD-160

EBSheriff
7-6-95

cc:
Orig. NDA 20-231
HFD-160/Division File
HFD-160/DivDir/Love
HFD-160/Chem/Stewart
HFD-160/MO/Hyman
HFD-160/Pharm/Meyers
HFD-160/Micro/Vincent
HFD-160/CSO/Rhee

NOV 22 1994

Division of Medical Imaging, Surgical and Dental Drug Products

Review of Chemistry, Manufacturing, and Controls

Reviewer: Patricia Stewart

NDA #: 20-231 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 6/30/94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-29-92	12-30-92	2-07-93
AMENDMENT	9-29-93	9-30-93	12-01-93
Filing Date	12/24/93		

NAME & ADDRESS OF APPLICANT: Colgate-Palmolive Company
909 River Road
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DRUG PRODUCT NAME

Proprietary: Colgate Total Toothpaste

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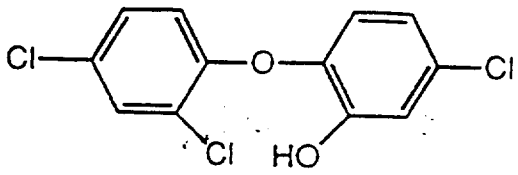
Molecular Weight: 289.6



Triclosan

Chemical Name: Sodium Fluoride

Molecular Formula: NaF

Molecular Weight: 41.99

SUPPORTING DOCUMENTS:

CONSULTS:

Environmental Assessment - acceptable 12/8/93
Labeling Committee - "Total" not appropriate in name.
Establishment Evaluation - Acceptable 6/16/94

REMARKS/COMMENTS:

This submission seeks FDA approval for Colgate Total (sodium fluoride USP 0.24%, triclosan 0.30%) Toothpaste in the United States with triclosan as the antiplaque and antigingivitis active ingredient. The FDA Labeling Committee did not approve of "Total" in the name. Proposed expiration 18 months.

CONCLUSIONS & RECOMMENDATIONS:

This submission is not approvable from a chemistry standpoint.

Patricia Stewart
Review Chemist, HFD-160

cc:
Orig. NDA 20-231
HFD-160/Division File
HFD-160/DivDir/Love
HFD-160/Chem/Stewart
HFD-160/DO/Hyman
HFD-160/CSO/Rhee

11-22-94

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20231

PHARMACOLOGY REVIEW(S)

NDA 20-231

Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

FEB - 4 1997

Norman A. See, Ph.D., R.Ph.
Draft completed: 1/27/97

Document Code AZ
Submission Date 1/13/97
Center Receipt Date 1/14/97

Sponsor: Colgate-Palmolive Co.

Drug: Total Toothpaste (0.3% triclosan)

Proposed Indication: Gingivitis

Related Drugs/INDs/NDAs: IND

Background Information: Colgate previously submitted the report of a mouse carcinogenicity bioassay (see Pharmacology review of amendment 068 to IND . Data from that study suggested that triclosan may cause liver tumors in mice when administered at dosages of 30, 100, or 200mg/kg/day. A dosage of 10mg/kg/day was a no adverse effect level (NOAEL) in that study. Members of the CDER Carcinogenicity Assessment Committee (CAC) expressed concern about these data, but stated that they would not be concerned if the sponsor could prove that the NOAEL in mice resulted in sufficiently high plasma levels of triclosan (relative to the clinically relevant level in humans) that the ratio of the AUC (area under the plasma concentration versus time curve) for triclosan in mice that received 10mg/kg/day to the AUC for triclosan in humans that utilized the maximum realistic dosage of Total toothpaste was at least 25. The significance of a 25-fold AUC ratio is that analysis of a FDA database revealed that this level of relative exposure equaled or exceeded the relative exposure achieved in more than 75% of the carcinogenicity bioassays that were conducted at the maximum-tolerated-dose (MTD). Achievement of this level of relative exposure is considered to be evidence that the dose with which the animal AUC data were obtained was sufficient to adequately test the carcinogenicity potential of the drug substance. However, the animal and clinical pharmacokinetic data that were available at the time of the CAC meeting were not adequate to permit such a comparison. Recently, the sponsor of NDA 20-231

conducted a study to better define the level of exposure to triclosan that occurred in mice dosed at 10mg/kg/day. These data are reviewed below.

Review of Nonclinical Data Contained in this Submission:

1. A pilot pharmacokinetic study of triclosan in mice following dietary administration, study No. 96-2489, in-life 10/96-11/96, conducted by
in compliance with Good Laboratory Practice regulations (21 CFR 58).

This study involved 50 male and 50 female CD-1 (ICR) BR mice (the same strain used in the triclosan bioassay). The animals consumed feed that contained triclosan, resulting in approximate dosages of 10mg/kg/day, for 14 consecutive days. Appropriate analyses of the feed were performed to ensure that the concentration and stability of triclosan in the feed were suitable. The parameters that were monitored included survival, clinical observations, body weight, food consumption, and the plasma concentration of triclosan. Blood samples were obtained from four animals per sex per time point:

Collection Intervals/Time Points

Day 1:	Predose
Day 4:	8am
Day 8:	8am
Day 12:	8am, noon, 4pm, 8pm
Day 13:	2am, 8am
Day 14:	8am

Blood was collected from lightly anesthetized animals via the retroorbital sinus; each animal was euthanized immediately after blood collection.

Results.
Survival and clinical signs. No remarkable observations.

Body weight and food consumption. No remarkable observations.

Estimated actual exposure levels. Based on nominal dietary concentration, body weight, and food consumption data, the mean intakes of triclosan were estimated to be (10mg/kg/day was targeted):

Males: 9.7, 10.2, 11.1, 9.7, and 9.9mg/kg/day on days 4, 8, 12, 13, and 14, respectively (the days of blood collection).

Females: 9.2, 9.5, 10.7, 9.9, and 9.5mg/kg/day on days 4, 8, 12, 13, and 14, respectively.

Mean plasma levels:

Plasma Concentrations (µg Triclosan/ml of Plasma

Day	Time	Males	Females	Combined
0	8:00	None	None	None
4	8:00	28.3	21.3	24.8
8	8:00	21.5	21.2	21.4
12	8:00	22.5	28.4	25.0
12	12:00	20.4	18.8	19.6
12	16:00	19.3	15.5	17.4
12	20:00	15.7	15.6	15.7
13	2:00	22.8	26.7	24.8
13	8:00	22.0	20.7	21.3
14	8:00	23.6	28.2	25.9

Note: The stated levels of "triclosan" refer to the concentration of "total" triclosan, meaning the combined values for free triclosan, triclosan sulfate, and triclosan glucuronide.

Summary/Discussion: The plasma concentration of triclosan remained fairly constant during the period observed, particularly at a given time point (e.g., 8:00am), indicating that the steady-state concentration was approached within 7 days of dosing. The reason the plasma concentration was not constant throughout a day is that mice only eat at night, and the triclosan was administered in the feed. Therefore, peak levels occurred at about 8:00am, when the lights turned on and feeding stopped, followed by a decline in the plasma concentration throughout the day until the next period of feeding started. The $AUC_{0-24\ hours}$ was calculated to be approximately 489,000ng•hr/ml (using the combined male/female data). Steady-state plasma concentrations were achieved in both males and females within 14 days; note that the plasma levels observed in this study are comparable to the levels observed in animals after 18 months of dosing at 10mg/kg/day in the bioassay (20.6±11.1µg/ml and 21.1±7.3µg/ml in males and females, respectively). These data appear to be

relevant to the conditions of the 18-month bioassay.

Regulatory Conclusion: The sponsor's estimation of the $AUC_{0-24\ hours}$ in mice that received 10mg/kg/day triclosan in the 18-month bioassay (489,000ng•hr/ml) is accepted.

Recommendations to the Sponsor: I have no comments to relate to the sponsor at this time.

1/27/97

Norman A. See

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 20-231
HFD-540 Div. File
HFD-540/PTL/JACOBS
HFD-540/PHARM/SEE
HFD-540/DO/HYMAN
HFD-540/CSO/BLATT

Concurrence Only:
HFD-540/DD/WILKIN 2/4/97
HFD-540/TL/JACOBS 1/29/97

Glatt

NDA 20-231

SEP 20 1996

Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540)

Norman A. See, Ph.D., R.Ph.
Draft completed: 9/4/96

Document Code BP
Submission Date 8/16/96
Center Receipt Date 8/20/96

Sponsor: Colgate-Palmolive Co.

Drug: Total Toothpaste (0.3% triclosan)

Proposed Indication: Gingivitis

Related Drugs/INDs/NDAs: IND 30,095

Background Information: Recently, concern was raised in regard to the levels of three of the specified impurities in triclosan

Summary/Discussion: I believe that the proposed specification limits for impurities of triclosan are acceptable.

Regulatory Conclusion: I recommend that the proposed specification limits for specified impurities of triclosan, as amended in the submission of 8/16/96, be accepted, and that within the context of NDA 20-231 concerns about impurities of triclosan be considered to have been resolved.

Recommendations to the Sponsor: I have no comments to relate to the sponsor at this time.

9/4/96

Norman A. See, Ph.D., R.Ph.
Reviewing Pharmacologist

cc:
NDA 20-231
HFD-540 Div. File
HFD-540/PTL/JACOBS
HFD-540/PHARM/SEE
HFD-540/DO/HYMAN
HFD-540/CHEM/VIDRA
HFD-540/CTL/DECAMP
HFD-540/CSO/BLATT

Concurrence Only:
HFD-540/DD/WILKIN 9/12/96
HFD-540/TL/JACOBS 9/4/96

Williams

NDA 20-231

JAN 19 1995

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Division of MISDDP: HFD-160

ORIGINAL SUMMARY

David E. Bailey, Ph.D.
January 18, 1995

ORIGINAL SUBMISSION DATE: December 30, 1992
LAST AMENDMENT DATE: October 27, 1994
DRAFT COMPLETED: September 19, 1994
REVISED DRAFT: December 16, 1994
SECOND REVISION: January 18, 1995

SPONSOR: COLGATE-PALMOLIVE Company, Piscataway, NJ

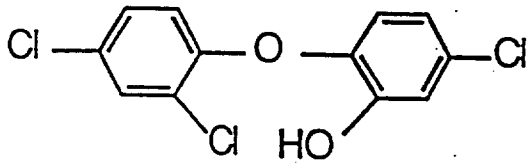
DRUG: Dentifrice - 0.24% Sodium fluoride; 0.3% Triclosan

PROPOSED INDICATION: Anticaries, gingivitis and antiplaque

RELATED SUBMISSIONS:

CHEMISTRY: Triclosan

Structural Formula:



Molecular Formula: $C_{12}H_7Cl_3O_2$

Molecular Weight: 289.6

Chemical Name: 2,2,4'-trichloro-2'-hydroxydiphenyl ether

5-chloro-2-(2,4-dichlorophenoxy) phenol

CAS Registry Number: 3380-34-5

Sodium Fluoride USP

CAS Registry Number: 07681-49-4

TABLE OF CONTENTS

LIST OF SUBMISSIONS

Submission	Date	Volumes
Original Submission	December 30, 1992	1.1-1.27 & 1.77-1.98
NDA Amendment	September 30, 1993	2.1-2.13
NDA Amendment	November 30, 1993	3.1
NDA Amendment	May 4, 1994	4.1
NDA Amendment	August 24, 1994	5.1
NDA Amendment	September 1, 1994	6.1
DMF(NDA) Amendment	October 27, 1994	7.1-7.25

FORMULATION

Components	Weight Percent
Triclosan	0.315
Sodium fluoride USP	0.243
Deionized water	
Dental type silica NF	
Glycerine USP	
Sorbitol, non-crystallizing	
Poly(methyl vinyl ether/maleic acid)	
Sodium lauryl sulfate NF	
Flavor	
Sodium hydroxide FCC	
Propylene glycol USP	
Titanium dioxide USP	
Carrageenan FCC	
Saccharin sodium USP	
Total	

BACKGROUND:

The Colgate-Palmolive Company has been developing this dentifrice containing triclosan and sodium fluoride under an IND. The bulk of the nonclinical safety data base for triclosan is contained in Drug Master File Number sponsored by . The DMF contains approximately 100 nonclinical studies where triclosan has been dosed by all routes of administration and a wide range of doses.

Many of the studies were conducted in the period of time from 1968-1979. All of the studies in the DMF have been reviewed at one time or another and by several different reviewers here at the Agency. Many of the studies were conducted prior to GLPs and not according to currently accepted protocols.

Colgate-Palmolive Company was asked to conduct studies in several different categories to fill data gaps in the DMF, and the studies were conducted and submitted, except for a Phase IV

On December 4, 1992, the Agency met with representatives of the Colgate-Palmolive Company at a pre-NDA meeting to discuss requirements for the NDA to be acceptable to the Agency. Later that month, the NDA was submitted by Colgate. The Sponsor had not incorporated some of the information that was requested, so the Agency refused to file the NDA.

In response to deficiencies, the Sponsor submitted additional data on September 30,1993. Userfees did not accompany the submission so the NDA was not filed until October 25, 1993. Additional nonclinical pharmacology and toxicology information was submitted November 30, 1993 and May 4, 1994.

The test material was not decoded in several nonclinical study reports. As requested by the Agency, that information was submitted by Colgate on August 24, 1994, and September 1, 1994. The DMF was updated by and this NDA was later amended by Colgate-Palmolive Company on October 27, 1994.

NONCLINICAL STUDIES:

FLUORIDE: The current position on the use of sodium fluoride in dentifrice materials is documented in the OTC monograph on anticaries drug products for human use (Fed. Reg 50 (189) 39854-39873, September 30, 1985). In this monograph, sodium fluoride used in dentifrices, gels and rinses is generally recognized as safe and effective as an anticaries drug product. The Advisory Review Panel assembled by FDA, concluded that sodium fluoride in a dentifrice product is safe and effective for OTC use as an anticaries agent when marketed in packages containing no more than a total of 260 mg of fluoride. Later, FDA approved the high fluoride dentifrice products that contain 1500 ppm fluoride.

Further review of fluoride safety data will not be conducted here.

TRICLOSAN: Most of the data in support of the safety of triclosan is Additionally, Colgate-Palmolive Company has completed several studies to update and fill in data gaps in the Also, the Sponsor of this NDA has agreed to conduct a Phase IV

Triclosan is widely used in a variety of consumer products primarily as a disinfectant and antibacterial in external use OTC products. In 1989, the European Community Cosmetic Directive approved triclosan at a level of 0.3% for use as a preservative in cosmetics, including oral care products. Dentifrices containing 0.2%-0.3% triclosan are internationally marketed in a number of countries.

Redacted 22

pages of trade

secret and/or

confidential

commercial

information

A THIRTEEN WEEK ORAL TOXICITY STUDY IN RATS VIA GASTRIC INTUBATION WITH ACTIVE MATERIALS A (37935) AND B (37928)

(Material A is the same as the Subject Dentifrice of this NDA)

AND

DETERMINATION OF TRICLOSAN AND ITS GLUCURONIDE AND SULFATE CONJUGATES IN RAT PLASMA BY GAS CHROMATOGRAPHY

Laboratory:

Report Date: 1990

Study Design

This study was conducted to assess the toxicity of Active Materials A (37935) and B (37928), which are both dentifrice formulations containing 0.3% Triclosan. Both compounds were administered orally, via gastric intubation to Sprague-Dawley rats. Treated animals were divided into six groups (30 rats/sex/group), three groups received formulation A and three groups received formulation B. Dose levels for both formulations were 0.40, 1.28, and 4.00 g/kg/day(1.2, 3.84, or 12 mg triclosan/kg/day). Three control groups (30 rats/sex/group) were used; one group received deionized water, a second group received placebo A at a dose level of 4.00 g/kg/day and a third group received placebo B at a dose level of 4.00 g/kg/day. Each group was divided into main study animals (20 rats/sex/group) which were kept for three months of study and satellite animals (10 rats/sex/group) which were designated for interim necropsy at 45 days. Clinical observations were conducted twice daily. Body weights were measured twice before study initiation, weekly during treatment and at sacrifice. Food consumption was measured weekly, beginning one week prior to treatment; food utilization was calculated pretest and weekly through 6 weeks for satellite animals and 13 weeks for main study animals. Fluid consumption was measured pretest and twice weekly thereafter. Clinical measurements, including hematology, clinical chemistry, and urinalysis were performed after 45 days of treatment for all surviving satellite animals and at approximately 90 days of treatment for up to 10 rats/sex/group of the main study animals. After 45 days of treatment for satellite animals and 90 days of treatment for main study animals,

all surviving animals were sacrificed, selected organs were weighed and organ/body weight and organ/brain weight ratios were calculated. Complete gross pathology examinations were conducted on all animals. Histopathology for the main study animals was conducted on selected tissues from all the animals in the placebo control and high dose groups and on selected tissues from rats found dead or sacrificed in a moribund condition from the deionized water control, low dose and mid dose groups. Histopathology of surviving animals from the deionized water control, low dose and mid dose groups was limited to sections of the stomach and other tissues with gross changes. Plasma of 5 animals/sex/dose was also analyzed for Irgacare MP following 90-days of treatment.

Reported Results

The distribution of deaths through the interim and terminal sacrifices was not suggestive of a compound A or B related effect. There were no treatment related clinical signs from administration of either formulation. There were no toxicologically significant changes in body weight in the interim or main study animals with either formulation. The food and fluid consumption was similar in groups receiving placebo or active materials. There were no toxicologically significant differences in food utilization between the placebo and active groups. Slight differences in hematology parameters between placebo A and B groups versus the vehicle control group were considered to be of no toxicologic significance. There were no treatment related differences in hematology parameters between the placebos and the respective active compounds at interim or terminal sacrifice. At interim sacrifice, any alterations in clinical chemistry parameters were slight, within an acceptable range of normal and were not considered to be treatment related. At terminal sacrifice, any alterations were either slight and within an acceptable range or statistically significant but sporadic and not attributed to treatment with the active compounds. There were no treatment related differences in the urinalysis parameters between Placebos A and B and the active A and B compounds, respectively. At interim and terminal sacrifice, there were several statistically significant differences between placebo controls and treated animals noted in several organ weights. The differences, however, were slight, did not occur with a dose relationship and were not considered to be toxicologically significant. Microscopic changes were observed in the stomachs of rats administered both the placebo and active materials. Changes noted in Placebo A and Active A groups included intracellular edema of the squamous epithelial cells at the limiting ridge, submucosal edema, eosinophilic intracytoplasmic inclusions in the glandular mucosa, hyperplasia and hyperkeratosis of the nonglandular mucosa and increased amounts of polymorphonuclear inflammatory cell infiltrations and a low incidence of necrosis or ulcers of the gastric mucosa.

ORAL MUCOSAL IRRITATION STUDY IN RATS

Laboratory:

Report Date: February 1991

Study Design:

The study was conducted to evaluate oral mucosal irritation potential of two -containing dentifrice formulations. One formulation was identical to the dentifrice that is the subject of this NDA. Dentifrices were applied once daily (1 g/kg) to the abraded and non-abraded oral mucosa of rats for 28 days. This was a parallel, placebo-controlled study with addition of positive control (5% sodium lauryl sulfate) and negative (distilled water) control groups. Groups consisted of 16 animals/sex. There were animal sacrifices on study days 2, 5, 14 and 28 days. In groups with observations of irritation on day 28, half the surviving animals were allowed an additional 7 day recovery period after completion of dosing. These animals then were sacrificed. Appropriate oral mucosal sites from animals of each treatment period were examined macroscopically and microscopically for evidence of irritation.

Reported Results

All animals survived until scheduled sacrifice times. Adequacy and uniformity of abrasions was confirmed at the day 2 sacrifice. There were no systemic, treatment-related observations. Macroscopic pathology findings observed in all study groups were limited to the oral mucosa (buccal). One rat from one of the abraded groups (active dentifrice) exhibited slight irritation of the labial junction prior to the day 2 sacrifice. No other irritation was observed. Incidences of slight irritation were noted sporadically in all intact study groups throughout the four sacrifice intervals. There was a higher frequency of these observations at the 2-day and 5-day intervals. The frequency was decreased by the 14-day interval. In conclusion, there were no macroscopic or microscopic observations which were related to specific irritant effects of the

Reviewer's Comment

Animal exposure occurred only once daily, while human use may be 3-4 times daily, therefore, the study does not completely support safety of clinical use. However, currently available clinical data adequately bridge this gap.

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