

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

FDA Request for Data and Information: Triclosan

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

Attachment 1

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

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I. Introduction

A review of the TEA submitted by Ciba Specialty Chemicals Corporation (Ciba), the published literature, and comments submitted and made at meetings of the Dental Products Panel convened by the FDA, shows that although several triclosan-containing formulations have been marketed globally, collectively, these formulations have not met the efficacy criteria for acceptance of triclosan as "generally recognized as effective" (GRAE). The only single active triclosan-containing oral care product that is effective is an NDA Drug Product approved to be both safe and effective by the U.S. FDA.

The criteria for classifying OTC drugs as "generally recognized as effective" are:

Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in §314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered. General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data. 21 CFR 330.10(a)

In this submission, we will:

- discuss the lack of published clinical studies documenting the general recognition of efficacy of triclosan,
- review the formula dependent characteristics of a triclosan-containing formulation that are necessary to deliver antiplaque and antigingivitis efficacy,

- discuss why triclosan is not generally recognized as having antiplaque and antigingivitis drug activity in products cited in the TEA, and
- discuss why the TEA process should not be used to undermine a proprietary NDA.

We will submit additional comments in a follow up submission which will further support our contention that triclosan is not GRAE. These comments will include expert opinions and other documentation to support our position.

We thus conclude that there are insufficient data to support the determination that triclosan meets the GRAE standard required for inclusion in a monograph. Furthermore, triclosan's formula dependent efficacy precludes a finding that triclosan is GRAE. Therefore, the TEA should be denied.

II. The Efficacy of Triclosan as an Antiplaque and Antigingivitis Active Ingredient is Formula Dependent, and a Variety of Triclosan-Containing Formulas Have Failed to Establish Triclosan as GRAE

Supra-gingival plaque control is important for the prevention of oral disease and maintenance of good oral health. More than two decades of academic and industrial research have been devoted to the development and evaluation of antiplaque and antigingivitis products. Yet, thousands of "person" years of laboratory research expended in the search for promising antiplaque compounds have not resulted in significant numbers of new therapeutic products that are clinically proven to be both safe and effective in long term studies [1-9]. Triclosan, in particular, has been the focus of many of these studies.

The published literature reveals that more than one hundred human clinical studies have been conducted to evaluate the potential effects of triclosan-containing systems in the oral cavity. Excluding studies on the aforementioned NDA Drug Product, Colgate Total®, the majority of these studies have been exploratory in nature, using multiple short duration (1-5 days) protocols and/or preliminary experimental formulas. Of the remaining studies, only twenty-five have been long-term (6-month or longer) clinical plaque and gingivitis studies. In these studies, triclosan has been formulated with a variety of ingredients, such as pyrophosphate, calcium carbonate, and zinc citrate.

We examine below the scientific evidence that exists for triclosan-containing oral care products. This evidence does not meet the GRAE standard.

A. Non-NDA Triclosan Formulations

1. Triclosan with Pyrophosphate

Five published clinical studies on formulations containing triclosan and pyrophosphate have shown either minimal efficacy or no efficacy for reduction or prevention of plaque and gingivitis. Some of these data were presented during the FDA OTC plaque and gingivitis monograph hearings, documenting that a formulation which contained triclosan and pyrophosphate was minimally effective or ineffective.

- In a 6-month study of the design factors for conduct of plaque and gingivitis studies, triclosan/pyrophosphate dentifrice showed a significant reduction in plaque (14.4%) at 3 months, but no effect on gingivitis at either 3 or 6 months. A sub-analysis of the gingivitis data suggested that reductions in gingivitis were measurable in a subset of subjects with high entry levels of gingival bleeding [10].
- In a 6-month study, the effects of 3 triclosan-containing toothpastes on plaque and gingivitis were compared. In this study, the triclosan/pyrophosphate dentifrice did not provide a significant reduction in either plaque or gingivitis compared to a placebo control [11].
- In a 7-month study, the effects of 3 triclosan-containing toothpastes on plaque, gingivitis and calculus were compared. The triclosan/pyrophosphate dentifrice provided a significant reduction (25%) in gingival bleeding, but there was no significant reduction in plaque compared to a placebo control [12].
- In a 6-month study, triclosan/pyrophosphate toothpaste provided a significant reduction in plaque (13.9%), but there was no significant reduction in gingivitis compared to a placebo control [13].
- Two 3-week experimental gingivitis studies both showed that triclosan/pyrophosphate toothpaste did not significantly reduce plaque accumulation or induced gingivitis compared to a placebo control [14].

The evidence for triclosan and pyrophosphate shows minimal or no efficacy. Thus, it cannot support “general recognition” among experts as to efficacy for antigingivitis and antiplaque indications.

2. Triclosan with Calcium Carbonate and Calcium Glycerophosphate

The efficacy of two triclosan-containing products formulated with different calcium carbonate components and calcium glycerophosphate was tested in a 3-month clinical study. The formulas showed significantly different levels of efficacy for both plaque and gingivitis, providing further documentation for the formula specific nature of triclosan activity [15].

Triclosan with calcium salts is not supported by significant or consistent scientific reports to demonstrate a “general recognition” of efficacy.

3. Triclosan with Potassium Salts

A number of products marketed outside the United States contain triclosan formulated with potassium salts (an active ingredient for use in treatment of hypersensitivity). To date, there have been neither 6-month controlled clinical data published nor short-term clinical data published to support the antiplaque and antigingivitis efficacy of these formulations.

Triclosan formulated with potassium salts has not been demonstrated to be “generally recognized” as efficacious.

B. A Formula with Substantiated Clinical Efficacy

There is only one oral care product with triclosan as the sole antiplaque and antigingivitis active ingredient that meets FDA standards for efficacy: Colgate Total®, an NDA drug product. The efficacy of Colgate-Palmolive’s patented formulation is supported by proprietary NDA data upon which the FDA cannot rely in a TEA proceeding.

III. Characteristics that Contribute to the Clinical Efficacy of a Triclosan-Containing Formulation, Demonstrating Why Triclosan's Formula Dependence Precludes the Establishment of Triclosan as GRAE

A. Properties of the Active Ingredient

The mechanism for delivery of antiplaque and antigingivitis actives into the oral cavity will be discussed below, as will the need for effective product formulation.

An effective antiplaque and antigingivitis active must do both of the following:

- be capable of delivery to the oral cavity and retention on the oral tissues for a sustained period after application [2, 16, 17]
- provide sustained biological activity *in vivo* by [18, 19]:
 - reducing the formation and growth of a pathogenic bio film on the tooth surfaces, i.e. dental plaque, and/or
 - reducing bacterial virulence factors and their consequences on the oral soft tissues.

Triclosan is well recognized as a broad spectrum antibacterial active with the potential to act in a multifunctional manner on oral bacteria *in vivo* [18]. More recently, triclosan has been demonstrated to possess anti-inflammatory properties [20, 21]. At concentrations above its Minimum Inhibitory Concentration (typically in the range 0.1 – 5 µg/ml for oral bacteria), triclosan is well recognized to be bactericidal [22, 23]. At significantly lower concentrations, it has been suggested that triclosan is bacteriostatic. Mechanistic studies have shown that the cytoplasmic membrane is the major target for triclosan action [18, 24, 25]. At high concentrations, triclosan induces membrane lesions that lead to bacterial cell death. At low concentrations, triclosan has been demonstrated to inhibit gross membrane function, such as the uptake and metabolism of glucose [18, 19]. More recently, detailed laboratory studies have suggested that very low levels of triclosan may inhibit single enzymes, such as enoyl reductase [26].

However, triclosan can only exert this antimicrobial effect when used in a formulation that allows it to be substantive [2, 16, 17, 22].

B. Properties of an Effective Delivery System

Toothpaste is an ideal vehicle because it can provide the user with multiple benefits in addition to antiplaque activity, such as fluoride for caries prevention. However, the chemistry of toothpaste formulations is highly complex, because of the large number of ingredients present, as well as the wide variety of chemical functionalities. In practice, this chemical complexity has been found to restrict the inclusion of many potential antiplaque and antigingivitis actives into toothpaste and/or mouth rinse [2].

A systematic review has recently been conducted into why so few potential antiplaque and antigingivitis actives meet the rigorous hurdles of achieving efficacy during drug development [2, 18].

The chemistries of the antiplaque and antigingivitis active and its formulation excipients must be fully compatible, and the product's micro-structure must positively reinforce delivery and retention of the active to deliver antiplaque and antigingivitis efficacy.

Moreover, to be clinically effective, the product vehicle must support:

- the effective release of the antiplaque and antigingivitis active into saliva during application (delivery),
- the effective uptake and retention of the antiplaque and antigingivitis active at oral receptor sites (substantivity), and
- a sustained level of biological activity between brushing occasions.

For product forms where the application time is short, such as toothpaste and mouth rinse, release of the active from the vehicle must be rapid (30-60 seconds). Such rapid release is generally favored when the active is in soluble form. A well known example of application of this principle was the selection of chlorhexidine digluconate for its high aqueous solubility for use in mouth rinse designed to prevent plaque and gingivitis [2, 16].

The uptake and retention of an active in the oral cavity are governed by the strength of the interactions between the active and its receptor sites and the rate of adsorption to and clearance from these sites. Dental plaque and the tooth pellicle are generally regarded as the more important sites of antiplaque and

antigingivitis activity, whereas the oral soft tissues are believed to act as reservoirs for antiplaque and antigingivitis actives [2, 16].

While a number of measures of activity have been quoted in the literature, such as fraction retained, salivary concentration, and retention half life, it is apparent that the most important parameter for sustained biological activity and clinical effectiveness is the concentration of an active in dental plaque over the extended time period between applications [16].

C. Properties of the Active Ingredient, Triclosan

Triclosan is poorly soluble in aqueous media, so it must be carefully formulated in an appropriate product vehicle to be clinically effective. Specifically, the triclosan can be co-solubilized with the flavor or solubilized in the surfactant phase of the dentifrice [2]. However, interaction of triclosan with excess surfactant or flavor reduces its chemical potential and, hence, compromises its adsorption onto oral surfaces and its binding to oral receptor sites. It has been established [2] that a balance between solubility, on the one hand, and bioavailability, on the other, is essential to ensure:

- optimal release of the triclosan from the formula during brushing,
- optimal retention and biological activity of the triclosan after brushing, and
- optimal clinical efficacy during regular use.

In comparison to other clinically effective antiplaque and antigingivitis actives, such as the cationic antibacterial agent, chlorhexidine, triclosan possesses "moderate" antibacterial activity [22, 27]. This has led researchers to seek unique ways to enhance the antiplaque and antigingivitis effectiveness of triclosan over and above the basic activity of triclosan alone.

D. Properties of an Effective Formulation

Mechanistic studies have shown that the PVM/MA copolymer in the aforementioned NDA Drug Product can significantly increase uptake of triclosan to hydroxyapatite and to gingival tissue. Clinical studies have also shown that elevated levels of triclosan are retained in the oral cavity between tooth brushing occasions and that these elevated levels provide sustained reductions in plaque

viability throughout these time periods contributing to a reduction in both plaque and gingivitis.

Other aspects of the formulation, such as the surfactant concentration, are critically important to this mechanism, and to the proven clinical efficacy of this formula on plaque and gingivitis. Therefore, the antiplaque and antigingivitis clinical efficacy of the triclosan/copolymer system is uniquely attributed to its specific formulation, i.e., the efficacy of triclosan is strictly formulation dependent.

Therefore, it is clear that the NDA Drug Product has been successfully formulated to accomplish the important balance between solubility and bioavailability of triclosan. Studies with other triclosan formulations have not demonstrated consistent or robust efficacy data.

IV. Triclosan in Combination with Another Antiplaque and Antigingivitis Active Ingredient

Products containing the combination of triclosan with zinc citrate have been demonstrated to deliver significant reductions of plaque and gingivitis in multiple 6-month studies. Short term plaque and gingivitis protocols, as well as mode of action studies, have clearly documented that the efficacy of the product results from the combined effects of the two antibacterial ingredients [12, 28-36]. Although an OTC Monograph drug may contain two or more safe and effective active ingredients as a combination, the combination of zinc citrate and triclosan together is not the subject of this TEA, and studies of this combination cannot be used to establish either ingredient alone as GRAE. Therefore, the data cited herein does not support triclosan as GRAE under the Antiplaque and Antigingivitis Monograph.

V. Information Submitted by Ciba in Its TEA Does Not Support, and in Fact Undermines, a Determination that Triclosan Meets the GRAE Standard

In addition, we would note that in Table 4, "Examples of Products and Labeling Claims in Selected Countries", of the TEA submitted by Ciba, other than Colgate Total®, an NDA Drug Product approved for antiplaque and antigingivitis activity, or toothpastes containing multiple antiplaque and antigingivitis active ingredients, none of the other toothpastes listed claim antigingivitis activity. Moreover, in the majority of countries listed in Table 1, "Countries Where Triclosan Sold or Marketed for Five Continuous

Years or More”, as “OTC/Cosmetic”, antiplaque claims are considered cosmetic. Again, excluding the NDA drug product or dual active ingredient toothpaste, triclosan has not been sold as a single active in a toothpaste claiming both antiplaque and antigingivitis activity. Therefore, based on Ciba’s own submission, triclosan does not meet the GRAE standard. On this basis alone the TEA should be denied.

VI. The TEA Process Is Not Intended to Undermine NDAs

Both Congress and the FDA have repeatedly acknowledged the importance of innovator research and clinical testing to the continued evolution of our nation’s health care system. The enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 underscored the value and significance of a New Drug Approval and set forth the limited conditions under which followers-on could market innovator drugs.

If Ciba or others wish to take advantage of Colgate-Palmolive’s research efforts, the law provides an avenue to do just that: an Abbreviated New Drug Application (ANDA) under section 505(j) of the Federal Food, Drug and Cosmetic Act. Since triclosan has been demonstrated to be effective only in Colgate-Palmolive’s patented NDA product, other adequately tested formulae would have to be presented in order for triclosan to be GRAE.

Colgate-Palmolive urges FDA to consider carefully the ramifications of its new TEA procedure on the NDA process. At issue here is, we submit, an attempted end-run around that process. Promulgation of the TEA process followed increased interest in bringing well-established “old drugs” to the U.S. market in a more expeditious manner than under the sometimes lengthy OTC monograph petition process. Drug products such as traditional Chinese herbs, or Kommission E Monograph herbs from Germany—ingredients marketed in many cases for centuries—were a large focus of the new procedure. While drugs marketed in the U.S. are also permitted for a TEA, particularly for prescription drugs with long-standing safety records, the TEA process was not intended to permit a supplier to isolate one part of an NDA formulation and then attempt to genericize the ingredient without filing an ANDA.

VII. Conclusion

There are insufficient published data to support the determination that triclosan-containing oral care products meet the GRAE standard. In addition, the formula dependent characteristics of a triclosan-containing formulation demonstrate why triclosan does not belong in the monograph.

A determination that triclosan meets the GRAE standard would mislead consumers, in that the consumer would assume efficacy equivalent to the NDA drug product, and would therefore be misled about comparative efficacy in the marketplace.

Excluding a proprietary NDA Drug Product and products containing combination active ingredients, the TEA submitted by Ciba fails to document that any other toothpastes have been marketed with both antiplaque and antigingivitis drug indications. Further, in the U.S. for those wishing to market a triclosan-containing toothpaste with these indications, there is already a regulatory route, the ANDA process.

For all of the reasons cited in this submission, the Ciba TEA should be denied.

Colgate-Palmolive will submit additional comments, which will, with FDA's prior concurrence, become part of this record.

VIII. References

The references are included in Attachment 2.