

Procter & Gamble

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February 20, 2004

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

Re: Docket No. 81N-033P, Oral Health Care Drug
Products for Over-the-Counter Human Use;
Antigingivitis/Antiplaque Drug Products;
Establishment of a Monograph; Proposed Rules

Dear Sir or Madam:

The Procter & Gamble Company, a leader in dental and oral care products, respectfully submits these additional comments in accord with the Reply Comment Period announced in the Advance Notice of Proposed Rulemaking, Extension of Comment Period for OTC Antigingivitis/Antiplaque Drug Products published August 25, 2003 in the *Federal Register* (FR Doc03-21669). As the manufacturer of the Crest[®] and Scope[®] family of oral care products, Procter & Gamble has a significant interest in the ongoing development of this monograph.

Procter & Gamble appreciates the opportunity to provide additional input for consideration in establishing the OTC Antigingivitis/Antiplaque Monograph. During the call-for-data period and the Subcommittee deliberations, Procter & Gamble submitted to the docket and presented to the Subcommittee a substantial amount of information related to two active ingredients under consideration as antigingivitis/antiplaque agents, stannous fluoride and cetylpyridinium chloride. Both of these active ingredients have subsequently been recommended to Category I status by the Plaque Subcommittee. This submission further augments the previous information supporting stannous fluoride and cetylpyridinium chloride (CPC) and provides our recommendations for the Agency to consider in the ongoing development of the OTC Tentative Final Monograph for Antigingivitis/Antiplaque Drug Products.

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Our comments are organized into five main sections within this document:

1. Executive Summary of Procter & Gamble recommendations
2. Discussion on lack of scientific evidence to justify the need to establish a minimum quantitative threshold for therapeutic plaque reduction
3. Reduction in plaque biomass, inhibition of plaque metabolism or reduction in plaque virulence are all synonymous with the term 'antiplaque'
4. Recommendation to follow due process for the on-going monograph review of antigingivitis/antiplaque agents
5. General Monograph considerations and request for labeling flexibility

Respectfully submitted on behalf of The Procter & Gamble Company



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1. Executive Summary of Procter & Gamble Recommendations to the Advanced Notice of Proposed Rulemaking

- Procter & Gamble recommends that properly qualified stand-alone antiplaque products should be considered as cosmetic and outside of the scope of this rule making. Furthermore, within a therapeutic context, a numerical threshold requirement to define the relevance of a plaque reduction does not make scientific sense given plaque mass cannot be closely equated with the extent of gingival inflammation. Procter & Gamble recommends that the Agency dismiss any consideration of a threshold requirement for an antiplaque benefit and continue to assess the merits of antigingivitis/antiplaque drug ingredients based on the relevant therapeutic outcome, namely, reduction in gingivitis.
- The characterization of achieving a meaningful 'plaque reduction', embraced by both the Plaque Subcommittee and the American Dental Association, further support the recommendation of Procter & Gamble that stannous fluoride is entitled to an antiplaque statement of identity and indication for use identical to those presently recommended for the other category I antigingivitis/antiplaque actives. Procter & Gamble asks the Agency to consider the preponderance of data supporting an antiplaque benefit for stannous fluoride and to harmonize the labeling for all the category I ingredients of this rulemaking.
- Procter & Gamble believes a thorough review of antigingivitis/antiplaque ingredients and supporting data has already been conducted. We recommend that this rulemaking proceed toward the Tentative Final Monograph in accordance with due process as outlined in 21CFR§330.10.

- Procter & Gamble request the FDA recognize the acronym 'CPC' as an alternative "established name" for cetylpyridinium chloride to be used on the drug product's principle display label. Procter & Gamble agrees full disclosure of the US Pharmacopoeia drug name should appear in the drug facts section of the label, but respectfully request the monograph include the option to use the well established, and accepted, name of CPC as the official established name of the drug in the statement of identity.

2. Quantification of Plaque Reduction is an Inappropriate Means of Characterizing the Clinical Relevance of an Antigingivitis Chemotherapeutic

Procter & Gamble believes it has not been generally established that a stand-alone antiplaque product necessarily offers a therapeutic benefit to consumers. In fact, Procter and Gamble, both individually and as part of the Consumer Healthcare Industry Task Group, recommended that FDA regard properly qualified stand-alone antiplaque products as cosmetic and not subject to this rule making. Procter & Gamble respectfully disagrees with the recommendation made by WhiteHill Oral Technologies, Inc. (1981N-0033P, C-13, Vol. 78, Pg. 4 (D)) suggesting the FDA should specify a performance test to evaluate stand-alone antiplaque products as well as require a minimal quantitative reduction in plaque ($\geq 20\%$) be achieved to establish a clinically relevant antiplaque therapeutic benefit. P&G believes that within a therapeutic context, the clinical relevance of a plaque reduction is established by the commensurate reduction in gingival inflammation. Furthermore, a numerical threshold requirement to define the therapeutic significance of plaque reduction does not make sense given the lack of correlation between plaque mass and the extent of gingival inflammation. This was clearly discussed by the Plaque Subcommittee¹:

The precise genera and species of microorganisms in each dental plaque may differ from individual to individual, site to site in the same individual, and within a specific site over time...

Plaques differ not only quantitatively but qualitatively in their bacterial composition.....This difference in bacterial composition has a major effect on its pathogenic potential both for periodontal diseases and caries. Some dental plaques are not pathogenic or associated with disease...

The Subcommittee has no knowledge of any studies where the volume, mass or amount of plaque can be closely equated with the extent of gingival inflammation.

"The Subcommittee accepts that gingivitis is associated with an accumulation of plaque along the gingival margin but is unaware of any evidence that

¹ Federal Register. 68(103) at page 32236. May 29, 2003.

shows that there is a close correlation between the amount of plaque and the induction of gingivitis, as can be assessed using present day methods. It should be noted that the relationship between the quantity of plaque present and the degree of gingivitis is sufficiently complex such that reductions in plaque mass alone are inadequate to conclude that a therapeutic effect on gingivitis could be expected. Therefore, gingivitis reductions must be measured directly."

Plaque buildup can lead to the development of gingivitis and periodontal disease, but as indicated by the Plaque Subcommittee above, it does not invariably do so. On the contrary, "mouths can frequently be observed in which plaque is not associated with disease."^{2/} Scientific studies reviewed by the Plaque Subcommittee have provided evidence that some types of plaque are not related to gingivitis or other forms of gum disease at all.^{3/}

The American Dental Association, in their submitted comments to the docket (1981N-0033P, C-21, Vol. 86), offered strong support to the Subcommittee's conclusion that not all plaque reductions result in a therapeutic benefit. The ADA emphasized the following:

Not all plaque is located at the gingival margin, however, and it is possible that a product could have an effect to reduce plaque without having an effect on gingival health.

In summary, not all plaque reductions result in a therapeutic benefit. Likewise, the precise etiologic relationship between plaque mass and gingivitis has not been explicitly determined. Further, it is the recommendation of Procter & Gamble that properly qualified stand-alone antiplaque products should be considered as cosmetic and outside of the scope of this rule making. With respect to a therapeutic benefit, a numerical threshold requirement to define the

^{2/} Bowen, *The Prevention or Control of Dental Plaque*, in *Dental Plaque* 283 (W. McHugh ed. 1970). See also Bowen, *Future Directions for Dental Plaque Control Measures and Oral Hygiene Practices: Perspective II*, in *Dental Plaque Control Measures and Oral Hygiene Practices* 306 (H. Loe & D. Kleinman, ed. 1986)("[T]here is no simple, direct relationship between the accumulation of dental plaque and the onset of oral disease."); Ramfjord et al., *Oral Hygiene and Maintenance of Periodontal Support*, 53 *J. Periodontal* 26 ("In many children and some adults one may find definite plaque on the teeth without clinical evidence of gingivitis.").

^{3/} M. Pader, *Oral Hygiene Products and Practice* 69 (1988) and Federal Register 68(103) at page 32236. May 29, 2003.

relevance of a plaque reduction does not make scientific sense because plaque mass cannot be closely equated with the extent of gingival inflammation. As stated on numerous occasions by the Plaque Subcommittee and the American Dental Association, determining the clinical relevance of a therapeutic plaque reduction should be established by the concomitant reduction in gingival inflammation. As such, Procter & Gamble recommends that the Agency dismiss any consideration to require a quantifiable threshold for plaque reduction and continue to assess the merits of antigingivitis/antiplaque ingredients based on the relevant therapeutic outcome, namely, reduction in gingivitis.

3. Stannous Fluoride Provides Multiple Relevant and Meaningful Antiplaque Benefits Including Reductions in: Plaque Virulence, Plaque Composition, and Plaque Biomass

In the ANPR comments previously submitted by Procter & Gamble (1981N-0033P, C-14, Vol. 81), three relevant antiplaque mechanisms (reduced virulence, altered composition, mass reduction) were described, all of which can be characterized as providing an antiplaque benefit. With respect to stannous fluoride, disruption in plaque metabolism, reductions in plaque virulence as well as reduction in plaque biomass have been repeatedly demonstrated. The Subcommittee recognized that 'plaque reduction' is a generic term that extends beyond biomass reduction to also include reductions in plaque virulence⁴:

In general, the Subcommittee would also expect a reduction of dental plaque mass and/or plaque virulence (degree of pathogenicity as indicted by the severity of the disease produced)..... Where possible, additional evidence for the effectiveness of the agent should be provided by demonstrating a shift in the plaque flora.

The American Dental Association⁵ further emphasized the broader interpretation of 'plaque reduction' to also include metabolic inhibition and plaque bactericidal activity:

The ADA believes that agents that reduce gingivitis by either killing plaque bacteria or by reducing its metabolic activity should be permitted in OTC antigingivitis products.

The characterization of achieving a meaningful 'plaque reduction', embraced by both the Plaque Subcommittee and the American Dental Association, further support the recommendation of Procter & Gamble that stannous fluoride is entitled to an antiplaque statement of identity and indication for use identical to those presently recommended for the other Category I antigingivitis/antiplaque actives, cetylpyridinium chloride (CPC) and essential oils. Supporting evidence has already been submitted to the docket (1981N-0033P, C-14, Vol 81).

⁴ Federal Register. 68(103) at page 32246. May 29, 2003.

⁵ Docket 1981N-0033P, C-21, Vol. 86, November 24, 2003

Interestingly, another new six-month, double-blind clinical study, conducted in accordance with the American Dental Associations guidelines for evaluating the effectiveness of supragingival dental plaque and gingivitis control (1981N-0033P, C-16, Vol 84) offers additional supportive evidence of the antigingivitis and antiplaque benefits associated with stannous fluoride. This clinical data compliments other clinical findings and again demonstrates a significant effect on plaque mass reductions, in addition to previously reported significant reductions in plaque virulence and resultant pathogenicity.

Collectively, four six-month gingivitis clinical trials have been submitted to the Agency since the Subcommittee concluded their deliberations, all of which have demonstrated statistically significant reductions in plaque biomass with corresponding reductions in gingivitis exceeding 20%.

Procter & Gamble asks the Agency to consider the preponderance of data supporting an antiplaque benefit for stannous fluoride and in addition to the Subcommittee's recommended claim of "*helps interfere with harmful effects of plaque associated with gingivitis*", also allow the following indication:

"[bullet] helps [select among the following: 'control', 'reduce', 'prevent' and 'remove'] plaque that leads to [select one or more of the following: [bullet] gingivitis, '[bullet] gingivitis, an early form of gum disease,' or '[bullet] bleeding gums']."

Additionally, the statement of identity should also reflect the antiplaque benefit that has been clinically proven and is characteristic of stannous fluoride. Procter & Gamble recommends that the statement of identity be identical and consistent among all the Category I ingredients of this rule making, namely,

"antigingivitis/antiplaque" (optional: may include dosage form, e.g., dentifrice, toothpaste, mouthrinse).

4. Procter & Gamble Recommends that the On-going Development of the OTC Antigingivitis/Antiplaque Monograph Proceed in Accordance with Due Process as Outlined in 21CFR§330.10

Procter & Gamble believes a thorough review of antigingivitis/antiplaque ingredients and supporting data have already been conducted. This review began in August 1993 and concluded in December 1998 and entailed 27 days of presentations/deliberations.⁶ Despite the diligent effort amongst both industry and the Subcommittee at least one comment received prior to the November 25, 2003 ANPR comment deadline, requested that the FDA consider reconvening the Subcommittee panel to evaluate new data submitted to the docket (1981N-0033P). Procter & Gamble is not in general agreement to delay the Agency's review and ruling of this monograph and recommends that this rulemaking proceed in accordance with due process as outlined in 21CFR§330.10.

However, in the event the Agency determines there is "good cause" to reopen the administrative record and reconvene the expert panel to review additional comments and data relating to OTC antigingivitis/antiplaque drug products, Procter & Gamble request that the Agency provide a brief comment period (≤ 90 days) for submission of any new data generated up to that time. Further, it is recommended that comments previously submitted need not be resubmitted and additional comments should only address data provided/developed after December 1998 when the Subcommittee concluded their deliberations on antigingivitis/antiplaque ingredients.

⁶ Federal Register. 68(103) at page 32233. May 29, 2003.

5. Request for Administrative Flexibility in Finished Product Dosage Form, Directions for Use, and Labeling of Antigingivitis/Antiplaque Oral Care Rinse Products Marketed in Combination with an Anticaries Active Ingredient

The intent of the OTC Monograph system is to establish a thorough review of the active ingredient(s) utilized in OTC drug products, as opposed to a review of finished drug products that are approved via NDAs. This long-standing Agency philosophy has guided the development of many monographs. Furthermore, it has been recognized that monographs need to be flexible in terms of permissible dosage forms, directions for use and labeling so as not to limit ingenuity and product design.

DOSAGE FORM

For example, in the preamble to the OTC Anorectal Monograph⁷ published in the Federal Register, the following statement can be found, *“The panel did not intend to restrict ingenuity and product design as long as the product accomplishes the claimed effect and meet the same final formulation requirements of safety and effectiveness as any other dosage form. Other final monographs are similarly expansive in their permitted range of dosage forms.”*

It has also been recognized that the rationale for establishing permissible levels of an active ingredient in a different dosage form is best determined based on considering exposure, rather than concentration. For example, a dentifrice would always have a higher concentration of an active ingredient than a mouthrinse in order to deliver comparable levels of the active given a lower volume of dentifrice is used. Further, when establishing the upper limit of an active ingredient for a different dosage form utilizing the same route of administration, it is best to consider the milligram amount of the active to be delivered per dose rather than the concentration of active contained in the final product (ex., dentifrice would be ~10X more concentrated than a rinse to deliver the same exposure/dose).

⁷ Federal Resister: 53 at page 30756. August 15, 1988

Since safety has already been established for the actives, the upper allowable level of active in any oral dosage form should be based on the milligram amount contained in a delivered dose of the approved dosage form. The lower permissible level, on the other hand, should be governed by effectiveness as demonstrated through performance or clinical testing. If no validated study design or reference standard has been established, effectiveness through performance testing should consist of a single 6-month clinical trial satisfying the standards established by this rulemaking.

DIRECTIONS

Similar flexibility will be necessary when considering likely combinations with antigingivitis/antiplaque oral rinse products. For example, the inclusion of an anticaries active in combination with an antigingivitis/antiplaque active was recognized as rationale therapy by the Subcommittee and recommended for consideration by Agency. However, for oral rinse products, harmonization across the separate monographs is not achievable without flexibility or standardization amongst these monographs. For example, the anticaries final monograph directions for use require a 10ml oral rinse be used once or twice daily (depending on concentration) for 60 seconds and include directions to not eat or drink for 30 minutes after rinsing whereas the antigingivitis/antiplaque monograph recommends that a 20ml oral rinse be used twice daily for 30 seconds. The table below illustrates the comparison between the requirements of these monographs.

Comparative Assessment of Monograph Requirements for Oral Rinse Dosage Forms

	Anticaries Monograph 21 CFR §355	Antigingivitis/Antiplaque 21 CFR §356
Route of Administration	Topical Oral	Topical Oral
Active Concentration	0.02% (NaF)	0.045 – 0.1% (CPC)
Single dosage (ml)	10 ml	20 ml
Duration of use	60 seconds	30 seconds
Frequency of use	Twice Daily	Twice Daily

Reconciliation of these directions for use should be considered prior to the finalization of the Antigingivitis/Antiplaque Monograph to permit this rationale combination of therapeutic ingredients to be formulated in an oral rinse and be compliant with codified regulations. Procter & Gamble request the agency provide due consideration in resolving this disparity between these monographs for oral rinse products. For example, both monographs could provide the option of 15 ml rinse volumes used for 60 seconds, twice daily, under conditions of a combination anticaries and antigingivitis/antiplaque product.

LABELING NOMENCLATURE

There are many benefits to a uniform system of labeling names for drug ingredients, including the transparency provided to consumers as ingredients are identified by a single labeling name regardless of the origin of the product. In addition, health professionals in the medical community are ensured an orderly dissemination of scientific information, which helps to identify agents responsible for pharmacotherapeutic benefits as well as adverse reactions. Furthermore, scientists are ensured that information from scientific and other technical publications will be referenced by a uniform name and will not lead to confusion, misidentification, or loss of essential information.

For example, cetylpyridinium chloride (CPC) is also known technically by the following synonymous names: 1-Hexadecylpyridinium chloride monohydrate, 1-Palmitylpyridinium chloride, Pyridinium-, 1-Hexadecyl chloride, Acetoquat CPC. This ingredient is marketed under several common trade names such as: N-cetylpyridinium chloride monohydrate [Merck KGaA], CPC [Zeeland, Dishman], CPC Sumquat 6060 [Zeeland] and Chilsonated CPC [Zeeland]. All of these naming conventions are unified under the single Chemical Abstracts Service Registry number of 6004-24-6.

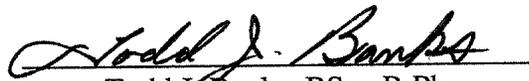
Cetylpyridinium chloride is a very complicated name that is difficult to pronounce and has no relevance to consumers. In fact, consumer research suggests consumers are confused and/or perplexed by this unfamiliar ingredient name. Therefore the pharmacopoeia nomenclature for cetylpyridinium chloride does not adhere to the consumer recognition principle of transparency

discussed above. A more easily associated and recognizable naming nomenclature would be preferable to both consumers and health professionals.

The Federal Food, Drug, and Cosmetic Act §508[§358] grants authority to the Secretary to designate an official name for any drug if he determines that an action is necessary or desirable in the interest of usefulness and simplicity. Procter & Gamble believes the name cetylpyridinium chloride is neither useful or simple to most consumers and thereby requests that the FDA work with the Secretary to modify the monograph to recognize the acronym 'CPC' as a simplified and useful alternative "established name" for use on drug product labeling.

CPC is readily associated with being synonymous with cetylpyridinium chloride. One need look no further than the Plaque Subcommittee deliberation transcripts where this ingredient was commonly referred to as CPC in discussions from industry and in dialog with the Subcommittee. Additionally, published literature frequently utilizes 'CPC' as an acronym for cetylpyridinium chloride as does the drug and cosmetic industry in general. Procter & Gamble agrees full disclosure of the US Pharmacopoeia drug name should appear in the drug facts section of the label, but respectfully request the monograph include the option to use the well established, and accepted, name of CPC as an official established name of the drug for use in the statement of identity on the principle display panel.

We ask that the Agency give careful consideration to these comments. If Procter & Gamble can be of further assistance, please do not hesitate to contact:


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