May 13, 1998

Mr. Robert Sherman
Center for Drug Evaluation and Research (HFD-560)
Attention Document Room
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Mr. Sherman:

I am forwarding, on behalf of Warner-Lambert Co., 25 copies of a position paper on the formulation of Category I antiplaque/antigingivitis ingredients in any appropriate oral dosage form; and appropriate performance tests for these formulations.

I would appreciate it if you will circulate this document to the members of the advisory panel prior to the May 27th-29th meeting for discussion at the upcoming session.

Thank you for your consideration of this request.

Very truly yours,

Robert Kirpitch
Director, Regulatory Affairs
Worldwide Consumer Healthcare

RK:dv

Enclosure
WARNER-LAMBERT COMPANY SUBMISSION IN SUPPORT OF INCLUSION IN THE FINAL MONOGRAPH OF ANY APPROPRIATE ORAL DOSAGE FORM OF CATEGORY I INGREDIENTS

Warner-Lambert Company ("Warner") makes this submission to support a determination by the Subcommittee that any Category I (generally recognized as safe and effective) antiplaque and/or antgingivitis active ingredient can be formulated in any appropriate oral dosage form. As explained more fully below:

1. It is common for FDA to determine that ingredients found to be Category I may be incorporated into any dosage form appropriate for delivery of the active ingredient to the site of action. Numerous examples may be found in different rulemakings covering topical and systemic OTC drug products. Part I of this document discusses tentative and final monographs for oral and topical administration of numerous Category I ingredients that reflect this concept. The same principle should apply to Category I antiplaque/antgingivitis active ingredients.

2. Different dosage forms may require different concentrations of an active ingredient which may not necessarily be in direct proportion to the volume of the dosage form. As discussed in Part II of this document, an appropriate oral dosage form containing Category I ingredients must fall within an upper safe dosage limit for the particular active ingredients. If no validated reference standard has been established, effectiveness through performance testing, should consist of a six month clinical trial satisfying standards utilized by the Subcommittee during this review until other, less extensive, performance tests can be validated and approved by FDA.

Warner requests that this Subcommittee affirm that Category I antiplaque/antgingivitis active ingredients may be formulated in any appropriate oral dosage forms under the conditions set out above.
PART I

UNDER OTC DRUG MONOGRAPHS FDA HAS HISTORICALLY DETERMINED THAT SAFE AND EFFECTIVE ACTIVE INGREDIENTS MAY BE FORMULATED IN A WIDE RANGE OF SUITABLE DOSAGE FORMS.

In a number of final and tentative final OTC drug monographs, FDA has determined that active ingredients determined to be generally recognized as safe and effective may be formulated in a wide range of appropriate dosage forms. These precedents are reviewed below.

A. Final Monographs

The active ingredients in many categories of OTC drug products approved under a final-monograph have been determined to be safe and effective without specifying particular dosage forms.

1. OTC Drugs Approved In A "Form Suitable For Oral Administration"

Several drug products have been approved in a "form suitable for oral administration," without further restriction on dosage forms. These are: (1) antacid drug products;\(\text{I}\) (2) antiflatulent drug products;\(\text{2}\) (3) antiemetic drug products;\(\text{3}\) (4) nighttime sleep-aid drug products;\(\text{4}\) (5) stimulant drug products;\(\text{5}\) (6) anthelminthic drug products;\(\text{6}\) (7) cholecystokinetic drug products;\(\text{7}\) and (8) deodorant drug products for internal use.\(\text{8}\)

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\(\text{I}\) 21 C.F.R. 331.1.
\(\text{2}\) 21 C.F.R. 332.1.
\(\text{3}\) 21 C.F.R. 336.1.
\(\text{4}\) 21 C.F.R. 338.1.
\(\text{5}\) 21 C.F.R. 340.1.
\(\text{6}\) 21 C.F.R. 357.101.
\(\text{7}\) 21 C.F.R. 357.201.
\(\text{8}\) 21 C.F.R. 357.801.
2. **OTC Drugs Approved In A “Form Suitable For Topical Administration“**

Drug products for several other conditions have been permitted under a final monograph "in a form suitable for topical administration," without further limitation as to dosage form. These are: (1) antifungal drug products;\(^\text{2}^\) (2) topical otic drug products;\(^\text{10}^\) (3) skin protectant drug products;\(^\text{11}^\) (4) external analgesic drug products;\(^\text{12}^\) and (5) pediculicide drug products.\(^\text{13}^\)

3. **OTC Drugs Approved In A Wide Range Of Appropriate Dosage Forms**

Several other final monographs permit the marketing of active ingredients in a wide range of dosage forms. For example, the final regulations for anorectal drug products state that the approved active ingredients are safe and effective "in a form suitable for external (topical) or intrarectal (rectal) administration,"\(^\text{14}^\) and list several permissible dosage forms, e.g., cream, lotion, or ointment.\(^\text{15}^\)

Moreover, FDA stated during the rulemaking proceedings that it did not intend to restrict the permissible range of dosage forms:

\[\text{[T]he Panel \ldots did not intend to restrict ingenuity in product design as long as the product accomplishes the claimed effect and met the same final formulation requirements of safety and effectiveness as any other dosage form.}\]

Other final monographs are similarly expansive in their permitted range of dosage forms.

The approved active ingredients in first aid antibiotic drug products are permitted "in a suitable ointment

\(^{2}\) 21 C.F.R. 333.201.

\(^{10}\) 21 C.F.R. 344.1.

\(^{11}\) 21 C.F.R. 347.1.

\(^{12}\) 21 C.F.R. 348.1.

\(^{13}\) 21 C.F.R. 358.601.

\(^{14}\) 21 C.F.R. 346.1.

\(^{15}\) 21 C.F.R. 346.50(a).

base” or a “suitable water soluble or oleaginous ointment base,” the approved active ingredients in topical acne drug products may be formulated as creams, gels, lotions, or ointments, and the approved active ingredients in wart remover drug products and in corn and callus drug products may be formulated either “in an appropriate nonaqueous solvent” or in a “fabric, plastic, or other suitable backing material.”

In the anticaries final monograph, FDA recognized several specific dosage forms: dentifrice, gel, rinse, tablets, and powder. FDA determined that these dosage forms would be considered safe and effective providing they met the biological testing requirements for animal caries reduction specified in the regulations.

During the rulemaking proceedings, FDA raised concerns about the safety of a powdered dosage form, and initially classified it as category III, because “the potential for a young child to accidentally consume a toxic amount of fluoride with a dentifrice in a powdered dosage form may be greater than with a paste dosage form.” Notwithstanding this safety concern, FDA ultimately recognized the safety and effectiveness of a powdered dosage form after reviewing additional studies that had been submitted to the agency. The agency also agreed with comments proposing that FDA recognize a wide range of fluoride dosage forms: “The agency agrees with the comment that an ‘anticaries drug’ can be formulated in various dosage forms and has defined numerous dosage forms in the final monograph.”

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177 21 C.F.R. 333.110.
179 21 C.F.R. 358.103 and 358.503.
180 21 C.F.R. 355.3.
181 21 C.F.R. 355.70.
B. Tentative Final Monographs

FDA's review of active ingredients in the context of ongoing rulemaking proceedings similarly supports the conclusion that FDA generally permits a wide range of dosage forms providing they meet specified performance testing requirements. For example, in the tentative final monograph (TFM) for OTC poison treatment drug products, FDA agreed to recognize dosage forms "other than aqueous solutions" providing that "suitable testing methods can be developed to insure that the final product meets USP XX standards for absorbency."\(^{25}\)

FDA has, on several occasions during rulemakings, taken the position that determining which specific dosage forms should be recognized as safe and effective is not a necessary part of the agency's rulemaking process. For example, in the TFM for analgesic, antipyretic, and antirheumatic drug products, FDA declined to recognize specific dosage forms on the basis that such action would be unnecessary.\(^{26}\) The agency also declined to make determinations regarding the relative safety of particular dosage forms, stating that such action would be outside the scope of monograph review.\(^{27}\) Instead, FDA proposed to recognize as safe and effective any analgesic-antipyretic drug product complying with the monograph's other requirements, as long as it is "in a form suitable for oral administration."\(^{28}\) Similarly, in the TFM for OTC health care antiseptic drug products, FDA declined to include the dosage form


One comment proposed that the following definition be included in § 343.3: "Powdered aspirin analgesic. A powdered form of aspirin packaged in individual unit doses."

The agency notes that the definitions recommended by the Panel in § 343.3 are general in nature and applicable to all dosage forms, and thus there would have been no reason for the Panel to include a definition of powdered aspirin. The agency sees no reason to include this definition, and, in order to conform with format and style of recently published monographs, the definition section is being revised in the tentative final monograph to contain only one definition: analgesic-antipyretic drug.

\(^{27}\) 53 Fed. Reg. at 46242 ("No attempt has been made in the tentative final monograph to compare the safety of dosage forms; such a comparison is not the intent of the OTC drug review.").

\(^{28}\) 53 Fed. Reg. at 46255 (proposed § 343.1).
"antimicrobial soap" on the basis that specific dosage forms would not be included in the final monograph "unless there is a particular safety or efficacy reason for doing so." Finally, in the TFM for OTC oral health care drug products FDA stated that any Category I oral health care active ingredient "may be formulated in any rational dosage form that is consistent with the directions for use of the product." FDA stated it was therefore "unnecessary to list specific dosage forms for oral health care drug products unless the dosage form is specifically relevant to the use, safety, or effectiveness of the ingredient."  

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PART II

SINCE DIFFERENT DOSAGE FORMS WILL REQUIRE DIFFERENT CONCENTRATIONS OF AN ACTIVE INGREDIENT, A SAFE CONCENTRATION SHOULD BE DEFINED FOR EACH CATEGORY I ACTIVE INGREDIENT AND A PERFORMANCE TEST OF EFFECTIVENESS SHOULD BE REQUIRED

Different ant plaque/antigingivitis dosage forms may contain different concentrations of active ingredients as demonstrated, for example, in the OTC anti-caries drug monograph. A dentifrice would always be expected to have a higher concentration of an active ingredient than a similarly effective rinse because a lower volume of product is used. A summary of representative active ingredients available in both mouthrinses and dentifrices is shown in the attached table (Attachment 1). The range of concentration of an active ingredient in a dentifrice displayed in this table is between 3.5 to 12.7 times that which exists in a mouthrinse. Triclosan was shown to be effective in a dentifrice at 10 times the concentration in a mouthrinse (0.3% vs. 0.03%) and chlorhexidine at 8.3 times the respective concentration in a mouthrinse. A prototype dentifrice containing 8 times the concentrations of the fixed combination of the four essential oils found in Listerine antiseptic mouthrinse was shown to significantly reduce plaque and gingivitis in a three week brushing model. The results of this clinical study were presented at the March 1998 American Association for Dental Research Annual Session (Attachment 2).

The concentration range of an active ingredient in any appropriate oral dosage form should be determined by both safety and effectiveness considerations. The safety of the product can be assured by specifying a maximum concentration or dose (mg) of each active ingredient. For example, the maximum concentration for essential oils in any dose form should not exceed the dose (mg) of these ingredients in the mouthrinse dose. Because the volume of dentifrice that is used is approximately 1/10 that of a mouthrinse (2ml versus 20ml), the concentration of active ingredient in dentifrice should not exceed 10 times that in the mouthrinse. Hence, for an essential oil containing dentifrice, the concentration of essential oils should be limited to 8-10 times that in a essential oil containing mouthrinse. The attached table (Attachment 3)
illustrates the dose of essential oils that is present in Listerine mouthrinse and that which would be present in an essential oil dentifrice formulated at 8 times and 10 times the concentration in the mouthrinse.

Efficacy considerations should dictate the minimum permissible concentration. Although the preference for performance testing would be for shorter, less extensive tests, such tests cannot reliably be used to demonstrate the effectiveness of a particular formulation of a Category I active ingredient until appropriate reference standards are validated. Consequently, any appropriate oral dosage form should be initially required to demonstrate effectiveness by validated performance testing. Where a validated reference standard has been established (e.g., Listerine for a mouth rinse), short term performance tests can be required. Where no such reference standard exists at this time, effectiveness should be demonstrated by performance testing consisting of what may be considered to be the “gold standard” of performance tests - a six month clinical trial conducted according to the standards utilized by this Subcommittee in reviewing Category I ingredients. At such time as a reference standard is established and less extensive performance tests are developed and validated, FDA may amend the requirement either administratively or through the petition process.
CONCLUSION

For the reasons set out above, Warner requests the Subcommittee to affirm that any Category 1 antiplaque/antigingivitis active ingredient may be formulated in any appropriate oral dosage form provided that the concentration of each active ingredient falls within a maximum safe level and the formulation passes a specified performance test. For dosage forms for which a validated reference standard has not yet been established, the performance testing should consist of a six month clinical trial utilizing standards previously adopted by this Subcommittee in reviewing data submitted on those ingredients.
### SUMMARY OF ACTIVE INGREDIENT MOUTHRINSE/DENTIFRICE RATIOS

<table>
<thead>
<tr>
<th>ANTIPLAQUE/ANTIGINGIVITIS AGENT</th>
<th>MOUTHRINSE</th>
<th>DENTIFRICE</th>
<th>RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorhexidine</td>
<td>0.12%(^1,2)</td>
<td>1.0% (Gel)(^3,4)</td>
<td>1:8.3</td>
</tr>
<tr>
<td>Triclosan</td>
<td>0.03%(^5,6)</td>
<td>0.3%(^7)</td>
<td>1:10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANTICARIES AGENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Fluoride</td>
</tr>
<tr>
<td>0.02</td>
</tr>
<tr>
<td>Stannous Fluoride</td>
</tr>
<tr>
<td>0.1%</td>
</tr>
</tbody>
</table>

\(^8\) 21 CFR Part 355.10 Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph, Final Rule.

This clinical study was conducted to evaluate the utility of a short-term brushing model for assessing the inhibition of supragingival plaque and gingivitis by a dentifrice formulation. Forty-two qualifying subjects entered and completed this double-blind, parallel group, controlled study. At baseline, subjects received an oral soft and hard tissue examination and gingivitis, bleeding and plaque were scored. Subjects received an oral prophylaxis and were randomly assigned an experimental essential oil-containing dentifrice or its vehicle control. Subjects brushed unsupervised for one minute, twice daily for three weeks after which all clinical examinations were repeated. All examinations were performed by one experienced examiner. Analyses of covariance were used to compare inter-group means for each of the three outcome variables. Compared to its vehicle control, the experimental dentifrice produced statistically significant (p<0.0001) reductions of 39.6% for plaque, 10.8% for gingivitis, and 65.4% for bleeding. The results of this study suggest that three weeks of conventional use of an antiplaque/antiGingivitis dentifrice may be an adequate duration to demonstrate effectiveness. Additional studies need to be conducted to evaluate the reliability of this model as a predictor of longer-term (six-month) study results.
Attachment III

**ESSENTIAL OILS CONCENTRATION IN CONVENTIONAL DOSES OF MOUTHWASH AND DENTIFRICE**

(Mg. per Dose)

<table>
<thead>
<tr>
<th></th>
<th>Mouthwash - 20 ml dose</th>
<th>Dentifrice - 2g. dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8X</td>
<td>10X</td>
</tr>
<tr>
<td>Thymol</td>
<td>12.8</td>
<td>10.2</td>
</tr>
<tr>
<td>Eucalyptol</td>
<td>18.4</td>
<td>14.7</td>
</tr>
<tr>
<td>Menthol</td>
<td>8.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Methyl Salicylate</td>
<td>12.0</td>
<td>9.6</td>
</tr>
</tbody>
</table>