DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 9 2001

Richard Bourne, Ph.D.
Director, Regulatory Affairs
Colgate-Palmolive Company
P.O. Box 1343
909 River Road
Piscataway, New Jersey 08855-1343

Re: Docket No. 80N-0042
Comment Nos. AMD3 and CP9

Dear Dr. Bourne:

This letter responds to the February 24, 2000, amendment (AMD3) to Colgate-Palmolive's citizen petition (CP9) filed under the above referenced docket. Your amendment concerns biological testing requirements included in the final monograph for over-the-counter (OTC) anticaries drug products (21 CFR part 355). You request that the Food and Drug Administration (FDA) accept the results of an intra-oral appliance (IOA) test in humans to demonstrate the effectiveness of three fluoride formulations in lieu of the animal caries reduction test required by the monograph. You submitted protocols for short-term and long-term IOA studies.

I. BACKGROUND

Your amendment is a follow-up to a previously submitted petition (Docket No. 80N-0042/CP9) that included two generic protocols for short-term and long-term IOA studies, but did not provide information regarding the specific dentifrices to be tested. In a letter dated May 5, 2000, the Agency denied that petition. As discussed in our response, although testing in human subjects wearing a removable dental appliance containing enamel chips appears to offer certain advantages, there is disagreement within the scientific community about whether the IOA model is an appropriate substitute for the animal caries reduction test. We encourage the development of alternative testing procedures and believe that the criticisms of the IOA model are not sufficient to conclude that this test is unacceptable. We do not have sufficient data at this time to amend the anticaries final monograph to include a standard IOA model as a substitute for the animal caries reduction test. However, we will continue to review alternative biological testing for specific dentifrice drug products on an individual basis.

II. COMMENTS

A. General Comments

1. Neither protocol contains sufficient detail to be acceptable.

2. The formulations of the specific products being tested, the placebo, and the active control should be provided. In addition, the petition should state which protocol will be used for each

dentifrice. We informed you in our May 5, 2000, letter that citizen petitions requesting acceptance of the IOA model should identify the specific dentifrice product being tested. The protocols you submitted are generic, and the test products are identified as "Colgate Anticavity – Blue," "Colgate Whitening – Green," and "Colgate Whitening – White." Because we are presently reviewing petitions to accept alternative testing on a product-specific basis, we need assurance that the marketed product is identical to the tested formulation.

3. The principal investigator for a dental trial involving human subjects should be a licensed dentist. You provided the names of the investigators but did not include their credentials. It is unclear from the list if any of the investigators are qualified. In addition, one investigator should be identified as the principal investigator.

4. Adequate demonstration of bioavailability of fluoride in the biological testing models for fluoride dentifrices requires that the test product be significantly superior to the placebo and not inferior to the reference standard. In the June 15, 1988, tentative final monograph for OTC anticaries drug products, statistical analysis of the biological tests is discussed as follows: "... appropriate statistical quality control criteria must be used for drug products" (53 FR 22430 at 22440). It is inappropriate to conclude equivalence or noninferiority based on observing a nonsignificant test result of the null hypothesis that there is no difference between the investigational product and the active comparator. Further, for noninferiority trials, the one-sided $(1-\alpha)$ interval should be used.[1]

B. Comments on the Long-Term Study Protocol

1. An inclusionary criterion is that two enamel specimens need to be accommodated. However, the Procedure section of the Informed Consent states that three specimens will be placed. This contradiction is not explained.

2. The randomization schedule for treatment assignment is identified as A, B, C, or D for each product tested. Because there are only three test products (placebo, positive control, and test dentifrice) with the washout period included as part of each assignment, it is unclear why four treatment groups are used.

3. The protocol specifies that dropouts will not be included in the data analysis. Although we believe that efforts should be made to follow all randomized subjects to reduce the impact of dropouts on the effectiveness results, dropouts that do occur must be evaluated for factors that selectively cause them to withdraw. The influence of dropouts on the effectiveness results depends upon the number of dropouts, the proportion of dropouts among the treatment groups, and the statistical approach used to handle these subjects. We recommend a sensitivity analysis to ensure that the results are robust relative to the method of handling dropouts.

4. The primary and secondary endpoints of the study are not specified.

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[1] See the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals (ICH) guidance *E9 Statistical Principles for Clinical Trials* (FDA, 1998), section 3.32.

5. Appropriate statistical testing to demonstrate noninferiority between the test product and the positive control should be described.

C. **Comments on the Short-Term Study Protocol**

1. Exclusionary criteria include (1) the use of antibiotics or medications affecting salivary flow rate and (2) regular use of medications or drugs "(penicillin, Novocain, codeine, aspirin, etc)." Exclusion of medications that affect salivary flow rate is logical. However, the drug exclusion factor should be unnecessary because an inclusion criterion is a specific value for both stimulated and unstimulated salivary flow. Elimination of subjects who regularly use medications or drugs would exclude nearly all subjects because fluoride dentifrices and antiperspirants are drugs. A specific list of excluded drugs should be provided. In addition, it is unclear why Novocain is on this list. These exclusionary criteria should be revised.

2. The protocol refers to a 1994 Colgate-Palmolive Research Report (No. 4095) for a description of a "loaded retainer." However, this report is not included in the petition. An explanation of the procedure and the necessary documentation or, preferably, a summary of the report should be included in the protocol.

3. The primary and secondary endpoints of the study are not adequately described.

4. The method for measuring the percentage mineral recovery from the enamel specimens should be described.

5. In contrast to your proposed long-term study, which identifies Fisher's Protected Least Significant Test as the specific analysis that is conducted "post hoc," you propose an unspecified "post hoc analysis" if statistically significant treatment differences are detected at the 5- percent level. This would allow potentially any number of tests, which would invalidate any significant results.

6. Appropriate statistical testing to demonstrate noninferiority between the test product and the positive control should be described.

7. The proposed short-term IOA study appears to test only remineralization. Although short-term demineralization studies are described elsewhere in the submission, no specific protocol for this type of IOA study is proposed.

III. CONCLUSION

You provide insufficient information for the Agency to conclude that the methodology presented in these protocols is acceptable. Accordingly, your petition is denied. Any comments should be

identified with the docket and comment numbers at the top of this letter and submitted in triplicate to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

I hope this information will be helpful.

Sincerely yours,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs