

Warner-Lambert Company
170 Tabor Road
Morris Plains, NJ 07950
973 540-3416
Fax: 973 540-4300
E-mail: p.giorgio.fontana@wl.com

Pier-Giorgio Fontana, M. Sc. Ph.D.
Senior Director
Global Regulatory Affairs
Worldwide Consumer Healthcare R&D

**WARNER
LAMBERT**

January 24, 2001

Charles Ganley, M.D.
Director
Division of Over-the-Counter Drug Products (HFD-560)
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, Building Two
Rockville, MD 20850

**Subject: Follow-up to November 28 teleconference
Study Validation Support for
Intraoral Caries Test (Protocol 936-9213)
Experimental Gingivitis Model (Protocol 931-1309)**

Dear Dr. Ganley:

Reference is made to Sponsor's submission of May 15, 2000 submitted to Docket No. 80N-0042 and 81N-0033, which contained the above two protocols and to the minutes for telephone conference calls on July 21 and November 28, 2000 between the Agency and the Sponsor.

Clinical study design and validation issues for the above two protocols were discussed during the above teleconferences. The Agency requested that the Sponsor provide it with information regarding differences between positive and negative controls as a study validation criterion. Support for the proposed differences is contained in this submission.

This submission contains Confidential/Trade Secret Information to which all claims of privilege and confidentiality are asserted in both statutory and common law. Further dissemination may only be made with the express written permission of Warner-Lambert Consumer Healthcare.

If you have any questions, or need further information, please contact Robert Kohler at 973-385-5419.

Sincerely,

P. Giorgio Fontana / by llivilly

P. Giorgio Fontana, Ph.D.
Senior Director
Global Regulatory Affairs, Quality Assurance
And Documentation

81N-0033

PR 7

JAN 25 2001
dys

3363
0115

The purpose of this document is to provide feedback to the Agency on three issues that were raised during the conference call of November 28, 2000 during which representatives of Warner-Lambert and FDA discussed clinical and statistical issues related to a proposed clinical study for Listerine with Fluoride.

The first two responses below are provided as follow-up to Agency comments originally provided by the Agency on July 21, 2000 and subsequently discussed on the November 28, 2000 teleconference.

I. Under the Intra-oral Appliance Model:

The Agency requested that the Sponsor provide a value for the difference of percent surface micro-hardness (SMH) recovery between positive and negative controls as a study validation criterion.

Following a review of the literature and discussion with outside experts, Sponsor proposes an absolute difference of 10% or greater of SMH recovery between the positive control and negative control. For example, if the negative control rinse exhibits a 10% recovery in SMH, it is reasonable to expect the positive control rinse to exhibit a recovery in SMH of 20% or greater.

The suggestion of a 10% difference of SMH recovery between the positive and negative control rinses is based primarily on experience of Dr. Domenick Zero, using dentifrices, in the intra-oral caries test. His review article, "In situ Caries Models" (Advances in Dental Research: 9 (3):214-230, 1995), a copy of which is in Appendix A, provides examples of data from four dentifrice studies in support of the Sponsor's recommendation. Based on the results for the gauze-covered ICT chips (Table I), it is reasonable to expect an absolute difference $\geq 10\%$ between the positive and negative controls.

Table I
Difference in Mean % SMH Recovery
from Dentifrice versus Negative Control

Study Number	Data Extracted From	Difference in Mean % SMH Recovery
I	Fig. 10B	12%
II	Fig. 10A	13%
III	Fig. 6, Fig. 10A	22%
IV	Fig. 10B, Fig. 11B	20%

* data from gauze covered remineralization model (Zero, 1995)

The above data were generated using procedures similar to those that Sponsor proposes to use for the ICT study.

II. Under the Experimental Gingivitis Model:

The Agency requested that the Sponsor propose a percent difference between positive and negative controls to serve as a criterion for study validation, and provide data to support the proposed difference.

As a result of the Agency's request, the Sponsor reviewed the study validation section in clinical study protocol 931-1309 section 9.1.3, page 9, submitted May 15, 2000, in the context of plaque and gingival index results from eleven studies which compared Listerine antiseptic mouthrinse to a negative control. These studies all used the experimental gingivitis model accepted for final

formulation testing by the Plaque Products Subcommittee. Based on our discussion with the Agency and subsequent reassessment of the data from these studies, we have modified our original proposal.

The plaque and gingival index results from eleven 2-week studies comparing Listerine mouthrinse to a negative control are summarized in Table II. The plaque reductions seen in these studies are representative of those seen in the 6-month efficacy trials which were reviewed by the Plaque Products Subcommittee. The gingivitis reductions seen in two-week studies are generally lower than those seen in longer-term studies; this is consistent with published clinical findings which indicate that gingivitis usually resolves over a longer period. It should be recalled that the rationale for the inclusion of a clinical study for final formulation testing of essential oil-containing mouthrinses was based on the need to confirm the activity of new formulations against plaque biofilms *in situ*. Moreover, the long-term efficacy trials for the essential oil-containing mouthrinse standard consistently demonstrated a positive correlation between plaque reduction and gingivitis reduction. As a result, the Sponsor proposes that the criterion for validation of the experimental gingivitis study be based on plaque reduction alone. Based on the results for the two-week studies, it is reasonable to expect the positive control to reduce plaque by $\geq 15\%$ compared to the negative control. Accordingly, the criterion proposed for study validation is that the standard essential oil mouthrinse formulation (positive control) produce $\geq 15\%$ reduction in plaque as compared to the negative control at the 2-week examination period.

Table II. Percentage Reduction* at Two Weeks

	N	Mean	S.D.	Minimum	25 th Percentile	Median	75 th Percentile	Maximum
Plaque	11	23.6	4.9	16.0	19.6	23.3	28.0	32.7
Gingivitis	1	9.4	6.0	3.7	4.6	8.1	11.7	24.7

* Reductions, relative to negative control, in ascending order for eleven studies:

Plaque: 16.0, 17.7, 19.6, 21.9, 23.1, 23.3, 23.9, 25.2, 28.0, 28.0, 32.7

Gingivitis: 3.7, 4.3, 4.6, 4.9, 7.9, 8.1, 10.1, 10.2, 11.7, 13.6, 24.7

III. Regarding a clarification of the Randomization Schedule:

The ICT study utilizes a three by three crossover design. Three treatments (e.g., A, B and C) will be administered in 3 periods. Six treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA) are planned, and each sequence will be randomly assigned to an equal number of subjects. Each subject will receive the three treatments following the sequence that is assigned. The timetable for visits and procedures is shown in Appendix A of each of the protocols.