DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Pier-Giorgio Fontana, M. Sc. Ph.D.
Senior Director Global Regulatory Affairs,
Quality Assurance and Documentation
Warner-Lambert Consumer Healthcare
Pfizer Inc.
201 Tabor Road
Morris Plains, New Jersey 07950

Re: Docket No. 80N-0042
Comment No. ~~LET48~~ PR3

Dear Dr. Fontana:

This is in response to your submission dated January 25, 2001, regarding proposed studies to support amendment of the final monograph for over-the-counter (OTC) anticaries drug products (21 CFR 355) to provide for a combination mouthrinse containing your currently marketed Listerine product and sodium fluoride. The submission responds to questions raised by agency representatives during a November 28, 2000, teleconference and is on file as LET48 in Docket No. 80N-0042 in the Dockets Management Branch.

At that teleconference, the agency sought clarification of the following: (1) The proposed threshold for clinical significance for demonstrating anticaries activity of the combination using an intraoral appliance (IOA) model, (2) the randomization scheme for the IOA study, and (3) a percent difference between test and placebo that would constitute a clinically significant improvement in an experimental gingivitis model. In a subsequent teleconference on May 8, 2001, you indicated that the IOA and experimental gingivitis studies have been completed but not unblinded or the results computed. (See minutes of May 8, 2001 teleconference coded as MT10 in Docket No. 80N-0042 in the Dockets Management Branch.)

The Division of OTC Drug Products has the following comments:

IOA Model:

1. A 10-percent change in surface micro-hardness between the placebo and the reference standard is acceptable for the IOA model.

2. Because the IOA study has been completed, it is too late to implement any change in the randomization scheme. The adequacy of the randomization scheme will be reviewed when the final study report is submitted.

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3. There is currently a lack of data demonstrating the effectiveness of aqueous solutions of sodium fluoride at pH's ranging from 4.2 to 7.0. Therefore, the IOA study, if successful, will only support the effectiveness of sodium fluoride 0.02 percent aqueous solution at a pH of 4.2 using a benzoic acid/sodium benzoate buffering system. Thus, 21 CFR 355.10(a)(3)(iii) of the anticaries monograph would be amended to: (1) Sodium fluoride 0.02 percent aqueous solution with a pH of approximately 7.0, and (2) sodium fluoride 0.02 percent aqueous solution at a pH of 4.2 using a benzoic acid/sodium benzoate buffering system.

Experimental Gingivitis Model:

1. An experimental gingivitis model has been conducted to demonstrate that the Listerine/fluoride combination will have antiplaque and antigingivitis activity at least as good as Listerine alone and better than a placebo. Based on your belief that a clinically significant difference (historically 20 percent) in the gingival index (GI) between the test product and placebo cannot be seen during a two-week experimental gingivitis study, you propose a 15-percent improvement in the plaque index (PI) as the only appropriate clinically significant difference between the combination rinse product and the negative control. This was an amendment to your original proposal which included PI and GI as primary endpoints.

Although the Dental Plaque Subcommittee (The Subcommittee) believed that use of an experimental gingivitis model to demonstrate the effectiveness of final formulations of OTC antiplaque/antigingivitis drug products was reasonable, the specifics of what constitutes a clinically relevant improvement were not discussed. However, the Subcommittee made it clear that plaque reduction on its own is not a therapeutic claim and is not necessarily a surrogate for gingivitis. Thus, we consider it premature to accept plaque reduction as the only outcome. Therefore, both GI and PI should be the primary endpoints. In addition, failure to reach a 20 percent improvement in GI may impact on the comparison between Listerine alone and the combination of Listerine and fluoride. A test period that is too short may fail to uncover a difference between groups, even if one exists.

Further, although final formulation testing may be used to demonstrate that minor formulation changes do not reduce the effectiveness of a marketed drug product, the addition of sodium fluoride to the fixed combination of essential oils is a significant formulation change. Not only is there the question of fluoride's potential interference with Listerine's antigingivitis activity, there is the potential for fluoride to have antigingivitis activity of its own. Therefore, the combination must be not be inferior to Listerine alone in terms of its gingivitis effects, and Listerine must be superior to fluoride alone in its antigingivitis effects. In order to establish these contentions, the clinical outcome of GI improvement should be assessed. Further, for the proposed study to demonstrate that Listerine with fluoride is better at reducing gingivitis than fluoride alone, you will need to provide evidence that a GI reduction of less than the historical 20 percent would adequately demonstrate the effectivness of the combination. Please

provide a justification for a percentage less than 20 for the improvement in GI that is sufficient to conclude that the gingivitis reduction is clinically significant.

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

Sincerely yours,

Charles Ganley, M.D.

Charles Ganley, M.D.
Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 6/26/01

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 80N-0042 (ANTICARIES)

TO: Dockets Management Branch, HFA-305

☒ The attached material should be placed on public display under the above referenced Docket No.

☒ This material should be cross-referenced to Comment No. ~~LET 48~~, MT10 PR3

Charles J. Ganley, M.D.

Attachment