

Pfizer Inc
170 Tabor Road
Morris Plains, NJ 07950
Tel 973 385 2000 Fax 973 385 3761



October 14, 2002

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

Attention: Dockets Management Branch
Food and Drug Administration
12420 Parklawn Drive, Room 1-23
Rockville, MD 20857

Subject: **Request for Feedback - Revised 6-Month Gingivitis Protocol**

Docket No. 80N-0042

**"Anticaries Drug Products for Over-the-Counter Human Use;
Final Monograph," 60(194) *Federal Register* 52474-52510,
October 6, 1995.**

Docket No. 81N-0033

**"Over-the-Counter Dental and Oral Health Care Drug Products
for Antiplaque Use; Safety and Efficacy Review," 55(182)
Federal Register 38560-38562, September 19, 1990.**

Dear Dr. Ganley:

Further to the August 27 feedback meeting on Listerine with Fluoride, we hereby enclose a revised protocol and are requesting Agency review and comment. This is consistent with the meeting action items, which were (1) for Pfizer to submit a revised 6-month gingivitis protocol, and (2) for FDA to provide comments on the revisions.

The following information is attached:

Attachment I: FDA Minutes of August 27, 2002 Feedback Meeting

Attachment II: Revised Protocol for 6-Month Gingivitis Study, dtd. 10/14/02

Attachment III: Previously Submitted Protocol for 6-Month Gingivitis Study, dtd. 6/25/02

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Agency Comments on Previous 6-Month Gingivitis Protocol

Below are the Agency's comments (taken from the August 27 mtg. minutes) on the previously submitted 6-month gingivitis protocol, together with Pfizer Consumer Healthcare's responses.

- Pfizer proposes that the current primary outcome meet the provision that both the plaque and gingival indexes in the test product, essential oil-containing mouthrinse with fluoride, are "at least as good as" the positive control, essential oil-containing mouthrinse without fluoride, and that they are significantly better than the hydroalcohol (vehicle) control. The proposed testing requires a statistically significant improvement in the GI of the test product over the vehicle; generally accepted guidelines also require a 20% difference in magnitude to fulfill clinical significance.

The study has been designed in accordance with the Clinical Protocol Guidelines in the ADA Acceptance Program Guidelines – Chemotherapeutic Products for Control of Gingivitis.

We are cognizant of the Agency's position with respect to clinical significance.

- The difference of 10% between negative control and active in the sample size calculation should be clarified. As discussed above, Pfizer needs to ensure that the sample size calculation also satisfies the 20% difference criterion.

The magnitudes of 10% difference for mean MGI and mean PI have been added to the protocol (Section 12.5, paragraph 2). The study is powered to detect a 10% difference, and the sample size provides even higher power to detect a 20% difference.

- The intent-to-treat (ITT) analysis should be primary for superiority comparison. The FDA recommends defining the ITT population as all randomized subjects who are dispensed the study drug, regardless of having any post-baseline or evaluable data. For the non-inferiority comparison, it is recommended that both ITT and per-protocol (PP) analyses be submitted. The PP population should be defined in the protocol.

These comments have been incorporated into sections 7.6 and 12.4 of the protocol.

- Subgroup efficacy analysis (by demographics and baseline characteristics) should be planned in the trial.

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The protocol has been modified in section 12.2 (last paragraph) to assess treatment trends in demographic subgroups.

- The protocol (page 24) states that any changes in the planned statistical methods would be documented in the integrated clinical/statistical report. The primary analysis methods should be pre-specified in the protocol to obtain FDA concurrence. It is difficult to make judgments concerning statistical methodologies that are not pre-specified in the protocol, as this would be a review issue.

This statement has been removed from the protocol.

- Since the study is a randomized trial, the patient's treatment allocation should be generated prior to the initiation of the trial. Patient demographic data should include the time/date of enrollment for each individual.

According to Pfizer SOP requirements, the randomization schedule for a blinded study is generated prior to packaging of clinical test materials and initiation of the study. Clarification of this issue is detailed in section 7.7.2 of the protocol. Patient demographic data will be collected at the screening visit on a case report form that will capture the date of enrollment. Time of day will not be captured since it is not relevant information for this particular study.

- Generally, for one pivotal trial to be acceptable for regulatory purposes, it should be a robust, multicenter trial. The proposed study is scheduled to take place in Ontario, Canada as a single center study. The trial should be multicenter (3 centers but can have one primary investigator).

The study will be conducted at three clinical trial centers: Canada, Florida and Ohio. Each center will have a principal investigator who will be responsible to ensure that the study procedures at each study center comply with ICH and FDA Good Clinical Practice standard. The principal investigator for a center may also function as the site's clinical examiner.

- The proposed analysis for the primary and the secondary efficacy endpoints based on the ANCOVA method is acceptable. As it is recommended that a multicenter trial be conducted, "center" effect should also be included in the ANCOVA. The treatment-by-center and treatment-by-smoking status interaction effect should be tested. The interaction effect should be tested at a significance level of 0.10 instead of 0.05.

These comments have been incorporated into the protocol, section 12.2, paragraph 1.

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- In the currently proposed protocol, individuals are excluded who 1) are pregnant, 2) have uncontrolled diabetes, 3) have orthodontic appliances or partial dentures, 4) have taken antibiotics within the past month or 5) have oral piercing. These individuals are being eliminated due to either the difficulty of recording accurate and reliable measurements on them, or due to the confounding that their condition has on gingivitis. Nonetheless, Pfizer is excluding individuals in an OTC evaluation who will have access to Listerine, and detailed labeling that would discuss their exclusion is usually not used for OTC drug products. Pfizer should reconsider inclusion of these subjects, or explain why it is crucial to exclude them.

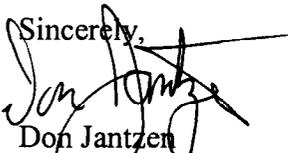
The inclusion/exclusion criteria have been modified to address these concerns. See Synopsis and sections 6.1 and 6.2.

- Pfizer should clarify a statement under Section 7.4 of the protocol (page 9 of Attachment 3) in which it is stated that "The examiner will not have access to the case report forms until the completion of the examinations."

The statement has been removed from the protocol. It is common practice in dental studies to prohibit examiner viewing of previous exam visit CRFs so that the examiner assessment of the current dental health status is not influenced by the knowledge of the dental health status of the previous visit's assessment.

We are anxious to receive the Agency's feedback on the revised protocol. Depending on the extent and nature of the comments this could be handled through a teleconference or, if minimal, through written communication. If there are any questions or if additional information is needed, please contact me at (973) 385-4637.

Sincerely,



Don Jantzen
Director, Regulatory Affairs
Oral Care & Gastrointestinal Products

Attachments

Desk copies (8) to Elaine Abraham, Project Manager
OTC Division-FDA