

MINUTES OF TELECONFERENCE

July 21, 2000

Corporate Building, Room S-300 2931 00 AUG 22 09:47

Subject: Issues Relating to Citizen Petition to Amend the Anticaries Final Monograph To Include an Oral Rinse Containing Fluoride and the Combination of Essential Oils in Warner-Lambert's Listerine Product.

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FDA Participants:

Division of OTC Drug Products (HFD-560)

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Division of Dermatological and Dental Drug Products (HFD-540)

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Warner-Lambert Participants:

Paul Okarma, Ph.D., Director, Regulatory Affairs

Tony Maguire, Ph.D., Biostatistics

Objective:

To discuss outstanding statistical issues concerning the sponsor's proposed studies to support the combination of fluoride and Listerine.

Discussion:

The Agency representatives inquired what statistical approach the sponsor was planning to use for the proposed intra-oral (IOA) study. The sponsor replied that the confidence interval approach was going to be utilized (i.e. 1-sided 95% CI). The Agency representatives commented that the 2-sided 95% CI approach is generally used for therapeutic clinical study analysis. The sponsor communicated that they believe the 95% CI approach is too stringent. The Agency representatives said that references could be faxed to the sponsor to help elucidate this issue.

In addition, the Agency discussed the following issues:

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MTB

Intraoral Appliance Model

1. The proposal was that the test is not greater than 20% worse than the reference standard. Please explain if the expected values from %SMH will make sense in this model. For example, if a 20% reduction is expected in caries between test and placebo, then 20% reduction could bring one back to the level of the placebo.
2. Measurements of the sponsor's proposed primary endpoint (%SMH) is based on collecting data from five different sites on each of the two enamel blocks and thus averaging these measurements. However, as the variability of the mean is less than that of the individual observations, one might end up having statistically significant results that are not clinically useful. As such, does a statistically significant but very small difference meaningfully validate the test, or should an appropriate minimum difference be specified?

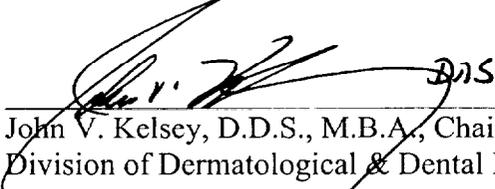
Experimental Gingivitis Model

1. For the confidence interval proposed, in comparing the GI and PI values between the reference standard and the test product, they were to be within 10% of each other. Please elaborate on how this will be calculated. If the GI value for the test product were 2.5, e.g., would the test product need to be within the range of 2.5 ± 0.25 ?
2. No amount of difference between the placebo and the other groups is specified as a validation for the trial. Is there a meaningful amount that should be specified to do so?

Action Items:

1. The Agency will send a list of references regarding the statistical confidence intervals issues to the sponsor.
2. The sponsor will submit a meeting request to the Agency along with the responses to the Agency's concerns.


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cc: HFD-560 Division File
HFD-560/Ganley/Katz/Parmelee/Lumpkins/Sherman
HFD-540/Cross, Jr./Kelsey/Hyman/Al-Osh

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References concerning for CI in equivalence trials

1. Fleiss, J.L (1992) General design issues in efficacy equivalency and superiority trials. *Journal of Periodontal Research* 27, 306-313.
2. Fleming, TR (1987). Treatment evaluation in active control studies, *Cancer Treatment Report*, 11, 1061-1065.
3. Huque et al (1998) Large sample inference for non-inferiority and clinical equivalence trials and the impact of multiple endpoints. *Proceeding of the ASA meetings*.
4. Tsong, Y. et al. (1999) An Overview of Equivalence Testing: CDER Reviewers' Perspectives, *Proceedings of Biopharmaceutical Section, ASA meetings*.
5. Chen, J.J (1999) Tests for equivalence between two proportions, *Drug Inf. Journal*