

Memorandum of Meeting

Meeting Date: June 6, 2000
Time: 11:30 a.m.
Location: Corporate Building, Conference Rooms S200A & B
Type of Meeting: Feedback Meeting
Subject: Anticaries
Meeting Chair: Robert Sherman
Meeting Recorder/Project Manager: Babette Merritt

FDA Participants:

Robert DeLap, Director, Office of Drug Evaluation V
Charles Ganley, M.D., Director, Division of Over-the-Counter Drug Products (DOTCDP)
Debbie Lumpkins, Team Leader, DOTCDP
Robert Sherman, Regulatory Review Biologist, DOTCDP
Gerald Rachanow, Esq., Regulatory Counsel, DOTCDP
Cazemiro Martin, Regulatory Review Chemist, DOTCDP
Martin M. Okun, M.D., Clinical Team Leader, Division of Dermatologic and Dental Drug Products (DDDP)
John V. Kelsey, D.D.S., M.B.A., Dental Team Leader, (DDDP)
Fred Hyman, D.D.S., M.P.H., Dental Officer, (DDDP)
Clarence C. Gilkes, D.D.S., Dental Officer, (DDDP)
James D. Vidra, Ph.D., Review Chemist, Division of New Drug Chemistry (DONDC)
Shiowjen Lee, Ph.D., Mathematical Statistician, Division of Biometrics IV (DOBIV)

Warner-Lambert Participants:

Scott Harper, Section Director
Paul Okarma, Director, Regulatory Affairs
Michael Barnett, Senior Director, Dental Affairs/Technology Development
Kon Fung, Senior Director, Statistics and Data Management
Tony McGuire, Senior Manager, Statistics and Data Management
Howard Rubin, Consultant
Jane Zhang, Oral Technologist
Duncan Yu, Research Associate
Lori Kumar, Director of Research Development
Domenick Zero, Director, Oral Health Research Institute, Indiana University School of Dentistry

Other Attendees:

Jeffrey Young, Reporter, Tan Sheet/FDC Reports
Jean Holland, Principal Scientist, JJCPWW

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Background: Warner-Lambert (WL) wishes to market an oral rinse product with anticaries, antiplaque, and antigingivitis claims (Listerine plus sodium fluoride).

Meeting Objective: To obtain Agency feedback and agreement on proposed studies to support amendment of the anticaries final monograph to include:

- 1) An oral rinse product containing sodium fluoride and the combination of essential oils in the company's Listerine mouthrinse.
- 2) An alternate dosing regimen and pH for the proposed combination mouthrinse.

Discussion:

WL stated that they are seeking concurrence that the five proposed studies (three caries, two plaque/gingivitis) will support an amendment of the anticaries monograph to include a combination fluoride and essential oil-containing rinse product with an alternate dosing regimen and at a different pH than is currently permitted. (See attached slides which were presented).

The Agency asked about the effect of adding neutral sodium fluoride (pH 7) to Listerine. If the resulting solution is at pH 4.2, this would involve a greater difference in pH than was originally proposed. WL replied that the product would not perform differently from the previously proposed product. In addition, WL stated that clinical data would demonstrate that the pH of the proposed product is not a critical factor.

The Agency asked whether the effects of greater fluoride uptake at a lower pH is this a concern. WL stated that although this may occur *in-vitro*, buffering in the mouth would negate this effect in actual use. WL further stated that fluorosis is not a concern in the population (12 years of age and older) that would use this product.

The Agency expressed concern about the ability of the proposed intra-oral appliance (IOA) study to demonstrate that the product is equivalent to a fluoride reference standard. The agency questioned the reliability of the IOA model to demonstrate fluoride bioavailability in dentifrices if, as WL asserted, it would be difficult to conduct an IOA study of sufficient size (number of subjects) to adequately demonstrate equivalence. WL indicated that they do not have experience with IOA studies involving more than 60 subjects. WL stated that there are logistical problems in controlling variables in large, multi-center studies and that they would have no more confidence that a larger study would provide any better results. WL stated that they have submitted a comprehensive package that addresses the Agency's concerns and, when viewed in total, the results of the five proposed studies would reach the intended endpoint. WL stated that they wish to move ahead with reasonable assurance that the citizens petition to amend the final monograph will be granted.

FDA stated that although a large IOA study may be difficult, there is no reason to believe that it cannot be done. If conducting such a study is a problem, the agency needs to know because of the increased interest in this test as a substitute for the rat caries test. The Agency stated that the rat caries study can be correlated with clinical trials. The agency expressed the concern that "if we move away from correlation with the clinical model, we're on a slippery slope." WL replied that although it is not impossible to conduct an IOA study of this size, it would be difficult. WL stated that they would consider the Agency's comments and submit a response, possibly a larger IOA study.

WL provided a brief description of the proposed statistical analysis for the IOA study. The proposal for the statistical analysis is a "least as good" test (similar to Schuirmann's test, but one-sided) comparing the proposed product with a reference standard. The agency stated that although it was willing to consider this methodology, the analysis would be evaluated by the FDA statistician.

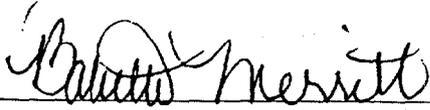
The Agency stated that the proposed rat caries and salivary clearance studies are not necessary. The Agency indicated they are seeking additional information on IOA studies and that any information would be helpful.

Conclusions:

1. The current proposal is not acceptable.
2. WL should propose an appropriately powered IOA study and provide a detailed statistical analysis plan.
3. WL should use an experimental gingivitis model to demonstrate that the addition of fluoride does not affect the antiplaque, antigingivitis efficacy of the essential oils.
4. The proposed rat caries and salivary clearance studies are not necessary.

Action Items:

1. WL will consider the Agency's comments and will submit a new proposal.
2. The Agency will review the proposed statistical analyses to determine if the proposed IOA model is adequate. The Agency will verify the sample size calculation.
3. The agency will complete the meeting minutes and forward the results of the statistician's review along with some minor additional comments that were not covered during the meeting.



Babette Merritt, Project Manager

Minutes Preparer



Robert Sherman, Review Biologist

Chair Concurrence

Attachment: Copies of slides presented by WL

cc: List of Attendees

Filename: Antica.rmm