TABLE 11

MEMORANDUM OF MEETING
Wednesday, August 25, 1993
10:00 AM-12:00 PM
Maryland Conference Room

Between: Nonprescription Drug Manufacturers Association Members and Guests:

Daniel Abraham, Thompson Medical Company, Inc.
Dianne Bach, Nonprescription Drug Manufacturers Association
Lawrence M. Brass, M.D., Yale University School of Medicine
Timothy R. Dring, CIBA-GEIGY Corporation
David Edelman, Sandoz Pharmaceuticals Corporation
Ralph I. Horwitz, M.D., Yale University School of Medicine
Azmi Nabulsi, Burroughs Wellcome Company
Richard A. Paul, M.D., Sandoz Pharmaceuticals Corporation
Jesselyn Pe, CIBA Consumer Pharmaceuticals
Dana Rothacker, Ph.D., Thompson Medical Company, Inc.
R. William Soller, Ph.D., Nonprescription Drug Manufacturers Association
Lorna C. Totman, Ph.D., Nonprescription Drug Manufacturers Association
Catherine Viscoli, Ph.D., Yale University School of Medicine
Barbara Waitman, Esq., Thompson Medical Company, Inc.

and FDA Representatives:

Robert Temple, M.D., Director, Office of Drug Evaluation I (HFD-100)
Robert O'Neill, Ph.D., Acting Director, Office of Epidemiology and Biostatistics (HFD-700)
Charles Anello, Sc.D., Office of Epidemiology and Biostatistics (HFD-700)
Joel Freiman, M.D., Acting Director, Epidemiology Branch (HFD-733)
David Graham, M.D., Epidemiology Branch (HFD-733)
Yi Tsong, Ph.D., Division of Biometrics (HFD-715)
Michael Weintraub, M.D., Director, Office of OTC Drug Evaluation (HFD-800)
Debra Bowen, M.D., Director, Medical Review Staff, Office of OTC Drug Evaluation (HFD-830)
William E. Gilbertson, Pharm. D., Director, Monograph Review Staff, Office of OTC Drug Evaluation (HFD-810)
Helen Cothran, Chief, Gastrointestinal and Contraceptive Drug Monographs Section, Office of OTC Drug Evaluation (HFD-814)

Robert Sherman, Gastrointestinal and Contraceptive Drug Monographs Section, Office of OTC Drug Evaluation (HFD-814)
Mathew T. Thomas, M.D., Division of Metabolism and Endocrine Drug Products (HFD-510)

Also Present:

John Briley, Washington Drug Letter
Jennifer Morgerman, FDC Reports

Subject: Protocol for a Case-Control Study of the Relationship Between Phenylpropanolamine (PPA) and Stroke

The meeting was held at the request of the Nonprescription Drug Manufacturers Association (NDMA) to discuss the agency's letter dated June 17, 1993, containing comments on NDMA's draft protocol for a population-based case-control study of the relationship between PPA use and hemorrhagic stroke. NDMA submitted the draft protocol in response to safety concerns regarding reports of PPA's association with cerebrovascular accidents which have arisen during FDA's review of PPA as an over-the-counter (OTC) weight control drug product.

Dr. Gilbertson stated that this was a public feedback meeting and gave a brief summary of recent events regarding the agency's review of PPA for OTC weight control use. Dr. Soller reviewed the issues for discussion based on the agency's June 17, 1993 letter. The issues included the definition of PPA exposure, the proper exposure window, the use of surrogate interviews, and the sample size and study power needed for the primary and secondary aims of the study.

Dr. Horwitz stated that the primary aim of the proposed study was to determine whether PPA users (both male and female), ages 18 to 54, compared to non-users, have an increased risk of hemorrhagic stroke. He stated that the secondary aim was to estimate an association separately by OTC indications for PPA, as a weight control drug product and as a cough-cold remedy. Dr. Graham stated that the agency was primarily interested in PPA use for weight control in women, ages 18 to 49, the population in which most of the cases of hemorrhagic stroke have been reported.

There was a general discussion concerning the merits of focusing on all OTC uses of PPA in all users ages 18 to 54 versus PPA use for weight control in women ages 18 to 49. Mr. Abraham stated that Thompson Medical Company was interested in the impact of PPA use and any associated risk in the whole population. Dr. Temple stated that the study should have two primary goals: (1) The risk associated with PPA use for weight control in women 18 to 49, and (2) the risk associated with all uses of PPA in the

whole population ages 18 to 54. Dr. Weintraub stated that so long as the study is adequately powered to achieve our goal, it is irrelevant whether the aims are labeled primary, co-primary, or secondary. Dr. Horwitz stated that, based on estimates derived from MRI market research data on PPA use, the study would be adequately powered at the start to respond to the primary and secondary aims.

Dr. Freiman stated that FDA believed that the proper exposure window was one day. Dr. Horwitz disagreed, arguing that focusing on strokes that occurred within 3 days of PPA exposure would be more appropriate and that cases should not be excluded from the study just because they were exposed to the drug more than 24 hours prior to the stroke. He stated that some strokes are not reported or diagnosed within 24 hours of exposure. Dr. Temple stated that the data indicate that the pressor effect (blood pressure elevation) disappears after the first day. He argued that if this is the mechanism for a stroke, the first day after exposure to PPA is the critical time period of interest. Ms. Waitman disagreed, stating that, based on a review of the case reports (excluding those with PPA-caffeine combinations), there were relatively few cases in which a stroke occurred after the first dose. Dr. Temple responded by noting that when the relation of the event to dosing was known, most occurred during the first day of medication. There was a general discussion regarding several studies of PPA's effect on blood pressure and whether the available data provide evidence of a first dose/first day effect. Included in this discussion was the increased number of cases that would be needed with a 1-day exposure window versus a 3-day exposure window. Dr. Soller reminded the group that practical considerations necessitated that the study be sized so that it could be completed in a reasonable amount of time.

The discussion turned to the use of surrogates in cases where a stroke patient was unable to respond to questions regarding drug use prior to the adverse event. Dr. Graham stated that if a surrogate was used to obtain information about a particular case, a surrogate should be used for the matched control. Dr. Horwitz strongly disagreed, arguing that using surrogates for the controls would be deliberately substituting less accurate information for more accurate information. Dr. Temple stated that using surrogates only for stroke cases would bias the study if identification of medication use was more complete in the controls.

There was a general discussion concerning an adequate sample size for the study. Dr. Freiman stated that the sample size would have to be substantially larger than originally proposed. In addition, an ongoing estimate of the exposure prevalence in controls should be performed to determine if any adjustments in sample size are necessary before the study is completed, as well

as an interim analysis to examine the possibility of high levels of risk that would preclude completion of the study. Dr. Soller stated that, based on comments in the agency's June 17, 1993 letter, an interim analysis was already planned.

Dr. Soller summarized the areas of agreement and issues that needed further discussion. He stated that the primary aim of the study will be to determine whether all PPA users, ages 18-54, compared to non-users, have an increased risk of stroke. Secondary or co-primary aims will be to estimate an association separately for weight control and cough-cold use, and to determine whether women, ages 18-49, using PPA for weight control, have an increased risk compared to non-users. In cases where it is necessary to interview a surrogate, a surrogate will also be used for the matched control. An ongoing estimate of exposure prevalence will be performed to determine whether the sample size is appropriate to achieve the primary and secondary aims of the study within the allotted time. An interim analysis will also be incorporated to examine the possibility of high levels of risk associated with PPA use. It was agreed that, prior to beginning the study, NDMA will submit a list of additional participating hospitals that will be included in the study. In addition, it was agreed that NDMA will calculate the sample sizes needed to meet the primary and secondary aims of the study using both a 3-day and a 1-day exposure window. Although it was tentatively agreed that, in order to reduce sample-size requirements, one-tailed tests of significance would be adequate to rule out the possibility of an association between PPA use and hemorrhagic stroke, NDMA will submit sample-size and power calculations for both one- and two-tailed scenarios. The issue of exposure window (i.e., 1 day vs. 3 days) will be resolved following FDA's review of NDMA's sample size estimates for relative risk ratios.

Robert Sherman

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