



Better Health
Through Responsible
Self-Medication

August 11, 1993

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Dear Dr. Gilbertson:

Enclosed with this letter is correspondence to FDA from Dr. Ralph I. Horwitz (Harold H. Hines Professor of Medicine and Epidemiology, School of Medicine, Yale University) which states NDMA's comments concerning FDA's feedback to NDMA regarding a draft protocol of an epidemiologic study on phenylpropanolamine (PPA).

In brief, the detailed comments to FDA from NDMA cover the following points, among others.

1. Definition of PPA exposures will be based on treating PPA products as a single exposure category in order to achieve the primary research objective, which is to examine the association of any PPA use and the risk of hemorrhagic stroke in subjects ages 18-54.

However, in order to assess an association for each type of PPA product (a secondary aim), the total sample size is augmented with a corresponding change in the power to detect elevated odds ratios separately for cough/cold remedies and appetite suppressants.

2. In order to address a concern that the medication exposure may not be biologically relevant to the stroke event yet recognize that case reports of stroke patients reporting prior PPA use up to a week earlier, the primary exposure window has been redefined as the three-day interval before the index event, with secondary analyses examining one-day and seven-day windows.
3. Because elimination of surrogate interviews could lead to a bias if PPA use were distributed differently among fatal or severe strokes rather than non-fatal or less severe strokes, dead patients or patients with impaired speech should not be excluded from the

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William E. Gilbertson, Pharm. D.
August 11, 1993
Page 2

study; consequently, data will be collected from surrogates of dead or impaired cases and from surrogates of their matched controls. (note: data from controls, all of whom are alive, will also be assembled by direct interviews).

- a. A value of .75 for the sensitivity of interviews with case surrogates is chosen and is reflected in all sample size estimations.
4. For the primary aim, examining the association between any PPA use and the risk of hemorrhagic stroke in subjects ages 18-54, 330 cases and 660 controls will be required. This calculation assumes a 3-day exposure window, 30% surrogate interviews among cases, an alpha level of .05, a beta of .8, and an attenuated Odds Ratio of 1.82.

However, in order to also address several secondary aims, the case sample will be augmented by 50%. Testing the power of the study to detect clinically important odds ratios with 500 cases and 1000 controls assuming a one-day exposure window yields: for any use of PPA, 69% for an OR of 1.82; 82% for an OR of 2.0; and 99% for an OR ≥ 3 .

A sample size of 500 cases and 1000 controls therefore provides adequate power for the primary aim of any PPA use, at the primary exposure window of 3 days and at secondary windows of 1 day and 7 days.

5. Additional sites could be added to the Yale-Connecticut Hospital Network in order to enroll 500 cases over 42 months.

We look forward to our meeting with FDA on August 25, 1993, at which time we will be prepared to discuss these issues in greater detail.

Sincerely yours,



R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology

Enclosure: Letter from Dr. Horwitz to Dr. Gilbertson on Behalf of the NDMA PPA Working Party dated August 9, 1993.

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