Summary of the Results of the Double Blind Identical Protocol Studies is as Follows.—

Favorable—6 clinical studies with 5 investigators.
Not favorable—2 studies.
Of no value—1 study.

CONCLUSION

It would seem that the data is adequate to support an appetite suppressant claims for this drug, Fenfluramine, provided the protocol is accepted by our Division of Statistical Analysis as adequate.

JAMES M. MOSER, Jr., M.D.

MEMORANDUM

FEBRUARY 17, 1970.

To: James M. Moser, M.D., Division of Neuropharmacological Drugs/OND (MD–120).
Thru: Acting Assistant Director for Scientific Coordination (MD–401). Acting Director, Division of Statistics (MD–450).
From: Peter G. James, M.D., Acting Chief, Statistical Analysis Branch.
Subject: Statistical evaluation of NDA 16–618 (Ponderex).

1. We acknowledge receipt of your request of January 5, 1970 for statistical evaluation of summary data contained in Vol. 4.1 of NDA 16–618. A detailed response to your request and a comprehensive analysis of these summary data is now being prepared.

2. Your request implied the existence of FDA criteria (both clinical and statistical) for the demonstration of appetite depressant properties of a drug and also made reference to nine (9) separate (well-controlled) clinical trials. Since neither of these is fully extant a detailed analysis and discussion became necessary to clarify these issues.

3. In the interim since review time has expired, a summary of the statistical findings is now submitted. It is based on our discussions and an overall view of the summary data and our findings. It is emphasized that no original case records of the individual studies were submitted for our examination and because of the limited time remaining when our review began none were requested. The issue of whether a series of studies were well-controlled, properly conducted and adhered to protocol sufficiently is often resolved by a close examination of the original clinical records and the clinician's entries.

4. We do not have nine (9) separate, well-controlled clinical trials in this submission. Four to five may be acceptable since they substantially adhered to the "standard" protocol and were relatively free of gaps in the treatment regimens and of doubts about missing data.

5. Pooling is not acceptable because we must examine enough findings from independent individual studies to assess a product's general performance on safety and efficacy over a variety of experimental situations.

6. Pooling is further negated because the "standard" protocol was not fully imlemented. A number of clinicians failed to follow the treatment regimens and to obtain the demographic and clinical population balance described in the protocol.

7. The data from the more acceptable studies appear to support a finding that the two drug treated groups data combined) lost more weight than their combined placebo counterparts for the first six weeks of medication. The advantage beyond the first six weeks is small. This fact plus the greater loss of patients beyond that point would be deterrents to a claim for a longer period of effectiveness, particularly if overweight loss is to be equated to anorexigenic properties and reference to this relationship is not included in the labeling.

8. At the sixth week all studies show some advantage of the drugs over the placebos. One study failed to hold this advantage and at the 12th week the placebos showed a slightly greater average weight loss. The study to study consistency which we seek appears to be present in this group of studies. The amount of advantage over placebo is not consistent, ranging from an average of 0.06 to 1.37 pounds per week for the six week period.

9. The high, variable dosage drug regimen appears to show greater advantage over its placebo control than the low fixed drug regimen. In making this comparison I have counted all full studies, including the questionable Gattereau and first Noble studies, because the number of patients in each group was small.