ANALYSIS OF DATA SUBMITTED BY MR. PRESTON

Introduction

A glance at Summary Tables A through G will show certain entries emphasized with Yellow crayon. This color emphasis was provided by Mr. Preston. He wished to demonstrate the following:

1. Table A. That initial starting weights were comparable for the placebo subjects and those in the several drug groups. He was not too happy with the data for the males, but tended to discount the differences because of small sample sizes.
2. Table B. The yellow entries are supposed to show that the average "% overweight" shown at the bottom of each table was comparable for all dosage groups and the placebo.
3. Tables C, D, and E. The yellow entries are supposed to show drug superiority in average weight loss for specific time periods.
4. Tables F and G. The yellow entries are supposed to show statistical significance for the drug groups.

Discussion

You will note that there are many yellow entries. Please be aware, also, that these tabular data represent an indiscriminate pooling of "controlled" studies.

After you and Dr. Knox have had an opportunity to examine more closely the material submitted by Mr. Preston, you may then wish to consider its official status also. Should the manner of submitting it through me be considered unacceptable, either as a procedure or as a rebuttal to the incomplete letter, you may wish to reject this material. You may wish to do this if the material is considered unacceptable clinical evidence or non-pertinent to the contents of the letter. In either or both instances you may not wish to read the balance of my report.

However,shoul d you believe that, eventually, we must accept this material, though through proper circumstances, and must also respond to the implications of efficacy suggested by the data and the yellow entries, then you may wish to read the evaluation and discussion of this material which follows:

At first glance the data in these tables suggest that the firm has made its points on clinical balance and consistent evidence of superiority over placebo. This advantage over placebo is considered to be sufficient evidence of superiority.

The premises and assumptions which the firm has incorporated into this statistical analysis of pooled data include the following:

1. Sample sizes will become larger, permitting more and better comparisons between the drugs being tested and between clinical and demographic subgroups within each of the groups of subjects being given each product under study.
2. That imbalances and differences within and between individual studies will sort of "wash out" or balance with respect to the following:
   (*a*) Diagnostic and demographic baselines
   (*b*) Population characteristics.
   (*c*) Protocols and study designs.
   (*d*) Dosage and treatment regimens.
3. The superiority of the drug will show through this mixture, if not clinically, then statistically.
4. The averages of the pooled data provide valid and unbiased measures of the drug's effectiveness and relative advantage over placebo.
5. Statistical tests of significance may validly be applied to pooled data and, with inflated sample sizes, have a greater chance of demonstrating that differences between the test products may be significant.
6. It is perfectly valid to compare results on placebo with those on four different dosage regimens and to test differences between them despite the fact that some studies in the pool contributed little or no information to these clinical comparisons and some studies had significant basic differences with respect to design, populations, duration, etc.
7. Consistent evidence (statistical in this instance) of advantage over placebo in demonstrating some weight loss, no matter what drug dosage or time period was followed, would prove clinical claims that the drug actually depresses appetite.

Assumption number 7 appears to be the key one for your consideration and seems to be the foundation for the firm's position. Can we accept, in a sense,