

extrapolations or generalizations from weight loss data as direct evidence of anorexigenic effects or properties of the drug? The problem is somewhat confounded by evidence that the placebo also produced small but consistent weight reductions. If this assumption is considered by your office not to be tenable with medical knowledge and our program requirements, then these data can be rejected and the matter is closed.

The remaining assumptions and the practice of pooling can be challenged on the basis of:

1. Common sense.
2. The requirements of the law with respect to substantial evidence from adequate, well controlled studies.
3. Our statistical paragraphs in the new law on medical advertising.
4. On the basis of generally accepted practices and principles of statistics.

Our first approach in responding to these data is to examine them as presented and see what they show and what they may hide. Next, we can apply some common sense and basic rules of experimentation and statistics to determine which studies and clinical (drug/placebo) comparisons are acceptable and present enough data to be acceptable on an individual study basis. We might even give the firm the benefit of the doubt and permit some pooling of acceptable data. This procedure I have followed.

#### *Table A*

This table shows the "initial" body weight. For the placebo subjects "initial" means exactly that, the first measurements taken at the beginning of the study. For the subjects in the various drug groups, the initial measurement can be different. For some it was the very first measurement, for others it could be the second, third, etc. measurement depending on the length of placebo period preceding drug use and the frequency with which measurements were taken.

This was done deliberately, according to Mr. Preston, in order to counter the effects of placebo which preceded drug use. However, this introduces a potential bias and some inconsistency in the procedure for handling data since some studies did not use a pre-drug placebo period. It is an example of the types of problems which can occur when dis-similar data and studies are pooled.

Even a cursory glance at Table A will reveal gaps and unequal sample groups. Relatively few male subjects were used. Some investigators used none at all. These factors all tend to detract from the meaning and acceptability of the totals and averages shown at the bottom of the table. For the moment, these doubts can be held in abeyance and the averages examined as presented.

There is an upward bias in the average starting weights of each base group that is related to the size of the dose used. The placebo subjects had the lowest and the 120 mg/day group the highest average. This is also true of the male subjects. This could be due to a number of factors: chance allocation of subjects, the unequal sample sizes in the studies, or an unconscious or conscious allocation of heavier, and perhaps more prone to lose, subjects to the drug groups.

An examination of the subsequent tables suggests that this bias is not fortuitous but persistent in the data and, as such, appears to place the placebo at a disadvantage, generally.

#### *Table B*

This table, for both females and males, shows a similar trend for the average *percent overweight*. This also generally increases with dosage level. The placebo group has relatively fewer overweight subjects and the higher dosages, the most. Thus we see in both Tables A and B evidence that the study groups may not have been properly balanced at the outset of these studies both with respect to base-lines and numerically. These are factors that must be taken into consideration in interpreting and evaluating the data on weight loss in the subsequent tables.

Tables C, D, and E show weight changes from "initial" body weights. In studying these tables one should be aware of another casualty of pooling—failure to provide concomitant clinical comparisons. The differences in the timing of initial weights, as mentioned earlier, prevents this type of clinical comparison. A change in body weight observed after two weeks on the placebo, for example, means specifically the first two weeks of the study. For subjects in the drug groups, this two week change can also refer to the change between the first and third weeks or between the second and fourth weeks of the study, etc. This factor of noncomparability also pervades Tables D and E which show weight changes at four and six week intervals from "initial" measurements.