meeting, and therefore could not speak with first-hand knowledge of what was said.

4. Concerning the contribution of components, it is our position that in order to justify the addition of one or more ingredients it is first necessary to demonstrate that these additions provide either greater safety or greater efficacy than a single component alone.

5. On page 3 you state that subtle differences can be shown in rigidly controlled animal experiments. At the May 3, 1968 meeting our view was expressed that the transposing of the effects obtained in animals to what might be expected to occur in man is not acceptable as hard data on which to base approval of a new drug application.

6. On page 3 you also state that you cannot obtain clear evidence of superiority and that you do not believe that you are required to. It is our position that although it is not necessary to demonstrate superiority in either safety or efficacy of single compounds as against previously approved single compounds, a different situation exists in the case of polypharmaceuticals. See paragraph 4 above.

7. On page 5 you state that to show contributions of component you submitted BIO–43 and BIO–47. In BIO–43 Dr. Schmitz used concomitant therapy, including diuretics. Under date of June 11, 1968, in connection with BIO–15 by Dr. Evangelista, you stated: "Since both treatment groups received the same concomitant drug it may be argued that this approach would still result in a valid comparison of active and non-active medication. However, this argument does not follow since there is no way of predicting what portion of the drug weight loss was due to diuresis or whether the combined therapy Bionamin and Diuril produced antagonistic pharmacologic actions." On the other hand, in connection with BIO–44 by Dr. Orchow, submitted under date of February 27, 1968, you stated: ". . . a large number of patients in each treatment group received concomitant drugs. Since in general the type of additional drugs is relatively the same for each group it is assumed that their use did not greatly influence the comparative analysis of the study results." These two quotations certainly appear to be contradictory, and raise the question as to whether the results reported by these two investigators influenced the arguments advanced. (Dr. Orchow in BIO–44 found that the average weight loss with Bionamin was 13.1 lbs while that with placebo was 8 lbs., whereas Dr. Evangelista in DIO–45 found that there was essentially no difference between the results achieved with Bionamin and the results achieved with placebo). On page 6 you refer to BIO–47 by Dr. Milton Cahn. This study ran for only 3 days, but you state that "a contribution for 3 days is still a contribution." In this connection your submission of July 3, 1968 states on page 00011 that "the average (albeit artificial) value of 5 calories per gram was applied to the difference in total intake. In this context, subjects treated with Bionamia exhibited a reduction in caloric intake of over 900 calories per day when compared to volunteers given Phentermine."

"The reduced caloric intake may be one explanation for the significantly greater mean weight loss observed in subjects treated with Bionamin."

Applying this same value of 5 cal./Cm. to other figures in Table I on page 00012, we arrive at, for example, an average intake of 7,795 cal. of solid food for the Placebo subjects for Day III.

The reported average weight loss for the three days was as follows:

	Pounds
Bionamin	3.9
Phentermine	2.3
Placebo	1.5

It is most unlikely that even on complete starvation one could lose more than a pound of adipose tissue a day; on the other hand, patients characteristically tend to retain fluids for the first week or so of a diet rather than to excrete more than the normal amount of fluid. Even if efficacy were demonstrated over a 3-day period, this would not be sufficient evidence of efficacy since a drug which was effective for only three days would be of no practical medical value in the treatment of obesity.

We request that you explain the discrepancies noted in your submission dated July 3, 1968.

8. On page 7 with regard to point #1, the fact to which we were drawing attention was that whereas in your submission of July 1, 1967 (page 0000062) the data indicate that the serum level values have fallen off sharply (in