

The summary for Dr. Bacon, pages 255 through 266, is obscure; page 262 appears to be totally extraneous.

Although the summaries bear a space for protocol number under Item 2, these have generally not been filled in, and I have yet to locate any protocol for Fisch, Rosenberg, Anderson, or Hollingsworth.

Most of the case report forms do not have the height or ideal weight recorded, so that the degree of obesity is unknown.

The claim that fenfluramine is a sedative rather than stimulant is questionable in view of Dr. Cagnon's article.

The 8 controlled studies submitted on 11/5/68 are all designated as Phase 2 studies. There are some designated Phase 3 but these are uncontrolled studies.

The weight losses recorded by Dr. Fisch and by Dr. Roginsky are almost inversely related to the dose of fenfluramine.

Most of the patients listed in this NDA lost too little weight to be considered as successful therapeutic responses.

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FOOD AND DRUG ADMINISTRATION,
Washington, D.C., September 8, 1969.

To: A. H. Robins Co.

NDA 16-618—Ponderex

Ponderex remains nonapprovable under (b) (1) as follows:

Lacking is substantial evidence for efficacy. Efficacy must be measured in terms of the amount of adipose tissue lost. The rate of weight loss is not a sufficient criterion unless the duration of treatment is adequately taken into account. It is further necessary to gain an approximate idea of the "ideal weight"; in order to do this the height as well as weight must be measured. On analyzing the controlled studies, we find that in 6/8 of the controlled studies the investigators reported average net weight losses of approximately 2 to 5 pounds, which is not a sufficient achievement to recommend the drug as a treatment for obesity. The duration in these studies varies from 2 to 8 weeks.

In 2/8 of the controlled studies where greater weight loss was reported, Hollingsworth recorded more weight loss (-12.8 lbs.) with placebo than any other investigator¹ following the use of fenfluramine; while Roginsky reported an average weight loss of -11.2 lbs. with only 40 mg per day dosage—a greater weight loss than any other investigator (except Hollingsworth) achieved using fenfluramine in doses up to and including 120 mg per day. Bacon reported a greater average weight loss (-4.8 lbs.) at the 20-60 mg level than Rosenberg or Fisch reported at the 120 mg level. Dr. Fisch showed less weight loss (-2.6 lbs.) at 120 mg dosage than any other group—except half of Dr. Bacon's patients, who are given 20-60 mg per day.

Examination of the uncontrolled studies cast further doubt on the validity of the evidence submitted. For example, Dr. Araujo in Mexico, Study #3028, reports an average weight loss of 36.5 lbs. in 8 weeks using only 50 mg fenfluramine per day whereas Dr. Berkowitz in this country reports only 8 lbs. weight loss in a 12 week study using 120 mg.

Dr. Berman voiced the opinion that the drug is poorly suited for general anorexic use (page 283).

Any attempt to dismiss these discrepancies by claiming population differences runs into the difficulty that, excepting abnormal pathological conditions, caloric requirement per square meter of body surface is almost identical from person to person providing the amount of exercise is the same and therefore it would be necessary to show that the groups which achieved greater weight loss also averaged much more exercise or ate much less food. No evidence has been presented that would lead us to believe that this is the case. Therefore we must conclude that the data fail to demonstrate a dose-response relationship. The practice of pooling data before analyzing it obscures the conflicting results obtained by the various investigators, and fails to give an adequate picture of the clinical findings.

As regards the claim that fenfluramine is not a central nervous system stimulant we note on page 186 that Dr. Gagnon stated: "... fenfluramine disturbs sleep and therefore a CNS stimulating action appears evident."

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¹ Except for some of Roginsky's patients on 60 mg dosage.