

September 21, 1971

Dr. Fred A. Clark, Jr.  
A. H. Robins Co.  
1407 Cummings Drive  
Richmond, Virginia

Dear Fred,

I have read the summary portion of the submission on *Pondimin* (fenfluramine), NDA 16-618 (vol. 4.1) with the following questions:

Is the presentation clear and does it substantiate the claims of the NDA;

Does the 'labelling' section present the data clearly and concisely, sufficient to convince the examiner that the claims for a new drug as 'safe' and 'effective' can be substantiated;

Are there additional studies that should be considered ?

My impression is that the summary is written poorly; that there is much redundancy, leaving an impression of 'padding'; and some important issues regarding anorexigenics are omitted (persistence of effects, tolerance, dependence, and similarity or dissimilarity to dextroamphetamine clinically). The summary is complete and sufficient in demonstrating that extensive pharmacologic, metabolic, toxicologic, and clinical studies were done. Indeed, the amount of data and number of studies are impressive. Yet, I can easily imagine the text inducing doubts. Some criticisms to be found in the details are:

the same data is presented in a variety of ways;

tables do not present the salient issues clearly;

whole sections appear as testimonials, diminishing the merit of the data base; and,

some language is obtuse, leading the examiner to focus on words rather than ideas.

There are two types of data that seem to be treated less adequately than one could wish. One issue is the use of the anorexigenics is the extent to which they inhibit appetite, reduce food intake (or increase metabolism) to yield a gradual loss in weight, and to do so *safely*. The criticism of dextroamphetamine is the short time it is effective (?tolerance), its abuse potential (?dependence), and the occasional toxicity expressed as insomnia, irritability and tremor. (The same can be said about other stimulating anorexigenics.) I find the comparison of fenfluramine and dextroamphetamine incomplete. The tables on pp. 28-33 are impressive but they lack clinical data. Perhaps the two drugs should be contrasted as to stimulation, secondary effects, abuse potential (has this been demonstrated or tested?), and dependence. Such a comparison could emphasize the unique properties of fenfluramine, make the labelling claims distinctive, and allow for approval as separate from the anxiety occasioned by dextroamphetamine abuse.

The second issue is duration of effect. A principal criticism of dextroamphetamine is a limited period of efficacy. These data do not allow for a decision as to whether continued use of fenfluramine is associated with tolerance, or whether weight loss is sustained. Are increasing doses necessary to sustain weight loss?

With regard to the labelling section, I find it adequate, clear, and useful as far as it goes. It is deficient in the issues cited above, although these answers may not be necessary for labelling.

I had an opportunity to discuss the conclusions of the FDA committee meeting on anorexigenics with Elmer Garner and Donald F. Klein. Both indicated that the agreement in the committee was limited; that no anorexigenic was really 'proven'; and none sustained weight loss. I inquired about the questions of tolerance and dependence, and these seemed the principal anxiety in approving new compounds. "Do we really need another drug to be abused?" I suggested fenfluramine may be significantly different than dextroamphetamine, and Dr. Gardner seemed attentive and interested. He said the FDA was about to allow an NDA for another anorexigenic, and he expressed the opinion that there was little reason to hold up an approval for fenfluramine.

My specific comments are attached. The volume is returned separately.

I am leaving for Europe and will return October 7. I have dictated and typed these notes rather hastily, knowing you wished a reply as soon as practical. My thanks for the opportunity to read these data, and I trust the submission will not fail. If I can be of help at the FDA, I have no hesitation to meet with them.

Sincerely yours,

Max Fink, M.D.  
Professor of Psychiatry