August 31, 1967.—"Incomplete" letter issues. No mention of clinical deficiencies. (7)

March 4, 1968.—I voice the opinion in a Division meeting that substantial evidence of efficacy was lacking for NDA 16–618; following this, the NDA was reassigned to me.

(*Volume 2.1*)

June 7, 1968.—The Director of Office of New Drugs phoned A. H. Robins and told them that ". . . Because of a more critical approach to the evaluation of anorexigenic agents we had again reviewed the clinical data available to support the efficacy of this product. They had been subjected to statistical review [3] and it was our conclusion that only one study, . . . supported the efficacy of this drug compared with a placebo. It was, therefore, felt that we could not recommend approval . . ." (8)

June 20, 1968.—An "inadequate" letter issues along the above lines. (9)

August 9, 1968.—The statistician wrote a 13-page memo pointing out numerous inadequacies in the data and its analysis. (10)

September 11, 1968.—In a conference with the sponsor I recommended that the package insert should contain a tabulation of the amounts of weight lost by the patients studied. (11)

(*Volume 3.1*)

November 4, 1968.—14 more volumes submitted.[4]

April 25, 1969.—The statistician's analysis of 8 controlled studies, submitted 11–4–68, states: ". . . at best, these studies are suggestive of a drug advantage over placebo." (13)

May 6, 1969.—My MOR of the November 4, 1968 submission recommends nonapproval on the grounds that substantial evidence of efficacy is still lacking. (14)

May 15, 1969.—Sponsor accuses Dr. Knox of bias. (15; page 5)

May 19, 1969.—My memo to Director (b) of DNDP re FDA policy on amphetamines includes a recommendation that the package insert and advertising contain tabulations of the actual total pounds of weight lost and the duration of therapy. (4)

June 17, 1969.—Sponsor requests that NDA be "withdrawn and resubmitted"—in order to avoid a non-approvable letter. (16)

September 9, 1969.—I submit a proposed "medical section" of letter (17) to sponsor which detailed many serious deficiencies in the NDA.[5]

October 2, 1969.—I discover that all the volumes of NDA 16–618 have been removed from my office without any prior notification or discussion with me. Upon enquiring as to their whereabouts, I am told by the Division Director (b) that he had had to reassign the NDA to another (the third) Reviewing MO because the sponsor had accused me of bias. I dispute the charge and point out that there is a danger in this type of reassignment, since it might place improper control of the review process in the hands of the sponsor. Nevertheless, the third MO (c) continues to review this NDA.

October 23 ,1969.—The third MO concludes in his MOR that the NDA was not approvable because 6 of the 7 controlled studies did not support the efficacy of fenfluramire. (18)

November 18, 1969.—My memo to the Acting Director (d), BuMed, includes a recommendation that the labeling for anorexigenics contain a factual statement as to the actual amount of weight loss achieved in the studies submitted in support of any given NDA. (4)

(*Volume 4.1*)

November 25, 1969.—9 more volumes submitted containing 9 additional studies (all following Protocal #25) by 8 different investigators.

December 29, 1969.—The third MO reviews the 11–25–69 submission and states that the data is now adequate to support an appetite suppressant claim provided the protocol is accepted by the Division of Statistics. (19)

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[3] I have been unable to find a written record of this review.

[4] A common practice of drug firms has been to respond to a disapproval letter with a deluge of additional volumes, which raises a question as to whether this is one of several forms of harassment. (12) The argument that the voluminous amendments were merely an attempt to provide more and better information must be examined in light of the nature of the material submitted and the circumstances surrounding each case.

[5] These recommendations were never incorporated into a letter to the sponsor; instead, the rough draft was returned to me 8 months later, without comment, by the Food & Drug Officer. (17)