MATERIAL FROM FOOD AND DRUG ADMINISTRATION FILES ON FENFLURAMINE (TRADE NAME: PONDIMIN, PONDEREX)

CHRONOLOGY OF NDA 16-618, PONDEREX, A. H. ROBINS

March 3, 1967: NDA 16-618 submitted.

August 29, 1967: Initial Medical Officer Review (MOR) by Dr. Zoppa, Public Health intern, states: ". . . claim that the drug is an appetite suppressant . . . would appear to be supported by the studies submitted."

No conclusion section included at end of review.

August 31, 1967: Dr. Hodges' "incomplete" letter based only on deficiencies under (b) (4) & (5)—no reservations expressed concerning the cliincal data.

June 7, 1968: Memo of Dr. Hodges' phone cal ito sponsor: can't approve NDA because Dr. Colmore's study is the only one which supported safety and efficacy. (At a Division meeting I had expressed my views on the method of evaluation of a drug for weight-reduction).

November 4, 1968: Vols. 3.1-3.14 submitted by sponsor.

November 8, 1968: Vols. 2.1-2.12 and 3.1-3.14 were delivered to my office (at Crystal Plaza, Arlington, Va.) for review.

April 25, 1969: Statistician's analysis of 8 studies requested by Dr. Knox: ". . . at best, these studies are suggestive of a drug advantage over placebo."

May 6, 1969: Dr. Knox' MOR concludes that sponsor has not provided substantial evidence of efficacy; recommends non-approval.

June 17, 1969: NDA withdrawn and resubmitted to avoid a non-approvable letter.

October 23, 1969: Dr. Moser's MOR. "Application was considered withdrawn on July 18, 1969, and reassigned[1] for review with respect to safety and efficacy."

"Conclusion: The application is incomplete and not approvable.

"Recommendations

"The firm perform two more well-controlled studies . . . "The claim that fenfluramine is less stimulating . . . is justified and should be included in the labeling."

November 25, 1969: Amendment to NDA includes 8 clinical studies.

December 29, 1969: Dr. Moser's MOR reviews submisson of 11-25-69 and states that data is adequate provided protocol is accepted by Div. of Statistics. (Notation at end of p. 7: "MD 120/JMMoser: ahe 2-2-70).

When Dr. Knox learned that an approvable letter was being sent to Dr. Simmons, he asked Dr. Moser for a copy of his MOR, and after reading it through noted that there was no statement under "Review of Individual Studies" concerning the number of lbs. of weight lost; each of the 8 studies was listed simply as "Favorable" or "Not favorable," without these terms' being defined. Dr. Knox pointed out this deficiency to several persons in the Bureau of Medicine; since no satisfactory response was received, Dr. Knox wrote a memo to Dr. Simmons expressing his concern re the lack of quantitative data in Dr. Moser's Review dated 12-29-69. Later, Dr. Knox checked the Divisional files to determine the status of this NDA, and found another version of Dr. Moser's MOR therein; this second one also carried the date, 12-29-69, on p. 1. The second version was almost identical in wording to the one first shown me, but at the bottom of p. 4, four additional lines were inserted, having to do with the amount of weight lost. (Notation at the bottom of p. 6: "MD 120/JMMoser: che—2-6-70."

February 17, 1970: Memo from Dep. Statistics to Dr. Moser expresses a number of reservations concerning the adequacy of the data.

March 30, 1970: Dr. Moser's MOR recommends approval of NDA.

June 24, 1970: NDA reassigned to Dr. Dobbs who had replaced Dr. Gibson as Div. Dir. of Neuro-pharmacologic Drugs. She estimates it will take 6 wks. to review the NDA.

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[1] All the volumes of this NDA had been removed from my office without prior notification to me. Upon enquiring, I was told by the Div. Dir. that he had to reassign the NDA to Dr. Moser because *the sponsor had accused me of being biased.* I pointed out that there was a danger in this type of reassignment, since it might place improper control of the review pricess in the hands of the sponsor.