A table of contents of the entire submission will be found in volume 4.1 beginning on page 10. In addition, each individual volume contains a table of contents to facilitate your review of this Application.

We trust that this new submission on fenfluramine will be found to contain data sufficient to permit approval of this New Drug Application by the Food and Drug Administration. We will appreciate being notified as promptly as feasible with respect to any questions concerning the Application.

Sincerely,

F. A. CLARK, Jr., M.D.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
PUBLIC HEALTH SERVICE,
FOOD AND DRUG ADMINISTRATION,
Rockville, Md., March 7, 1975.

DR. ALEXANDER M. SCHMIDT,
Commissioner of the Food and Drug Administration,
Room 14-81, Parklawn Building, Rockville, Md.

DEAR DR. SCHMIDT: In compliance with your letter of March 3, 1975, and in accordance with Mr. Allen T. Eaton's February 18, 1975, letter to you, I am enclosing additional material relevant to the issues raised at the Senate Sub-Committee on Administrative Practice and Procedure hearing on August 15, 1974.

Sincerely yours,

ROBERT O. KNOX, M.D.,
Medical Officer,
Division of Oncology and Radiopharmaceuticals.

DOCUMENTATION IN SUPPORT OF TESTIMONY GIVEN BY ROBERT O. KNOX, M.D.

1. INTRODUCTION

I jointed the FDA in August 1963 as a Medical Officer (MO) and was assigned to the review of New Drug Applications (NDAs) for a variety of drugs including "anorexiants."

Many of the clinical investigations were of dubious quality and contained questionable laboratory data (1)[1] and sponsors' summaries and analyses were often unreliable (1).

Substantial evidence of efficacy was lacking in the NDAs submitted for "anorexiants," but since many of the large firms already had their amphetamines on the market, failure to approve new NDA probably had little effect on the scale of manufacture and distribution. (2)

In 1958, "The Amphetamines—Their Actions and Uses," by Chauncey Leake, Ph.D., advanced the claim that amphetamines were both extremely useful in medical practice and free of toxic effects and other untoward consequences such as addiction.

Between 1963 and 1973 the only anoretic approved by the FDA was Pre-Sate, NDA 14-696; it had been assigned to another MO and was approved on April 20, 1965. A brief inspection of the Medical Officer Review (MOR) indicated that specific efficacy results by each investigator were not treated separately but, rather, general statements were relied upon—possibly quoted from the sponsor's summary. The average amount of weight loss demonstrated was less than 5 lbs.

In 1966, "The Amphetamines" by Oriana Kalant, Ph.D., expressed a very different view on the amphetamines and questioned Dr. Leake's claims. (3)

A great amount of activity has been manifested by the drug manufacturers in producing amphetamine congeners which have been claimed to have fewer undesirable adverse reactions than the amphetamines, but with the passage of time evidence has mounted indicating that the amphetamine derivatives share most of the disadvantages of the parent compound.

In spite of repeated urgings (4) over a period of several years that an FDA policy be established relative to the amphetamines, the BuMed did not formulate any policy. Of concern was the doubtful efficacy of these drugs, the potential for abuse, and failure of the package inserts to present a true picture of the poor efficacy usually achieved.

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[1] Numbers in parentheses refer to the items in the attached Appendix.