March 23, 1970: Representatives of the Company met with Drs. Gibson, D'Aguanno and Moser of the FDA to discuss the format and presentation of information in the package insert. Additional matters concerning the pharmacology were discussed by phone on March 24.

March 25, 1970: The Company submitted revised draft labeling containing all the information and changes agreed upon in the conferences with FDA. A new tradename, Pondimin, was used throughout the labeling.

April 27, 1970: Dr. Moser of the FDA called Dr. Dent to request minor changes in the labeling submitted on March 25. The next day Dr. Moser was notified by phone that the Company agreed to make the requested labeling changes.

May 20, 1970: Dr. Moser called Dr. Dent to inquire about the prevalence of depression among patients taking fenfluramine. He reported that Dr. Stanley Yolles, then Director of the National Institute of Mental Health (one of the NIH), had written an unsolicited letter to the Commissioner of Food and Drugs in which he reported that large numbers of patients in the UK had developed depression while taking fenfluramine.

June 9, 1970: In response to Dr. Yolles' charge concerning depression, the Company submitted a computer print-out of adverse reactions that had been reported to the Dunlop Committee in the UK (The Committee on the Safety of Drugs). This print-out was submitted to the FDA in triplicate and a fourth copy was delivered directly to Dr. Moser. According to the Dunlop Committee only 13 cases of depression had been reported from January 1964 through April 1970. We later learned that the Dunlop Committee had also sent a copy of the print-out directly to the Commissioner. Dr. Yolles, meanwhile, had been relieved of his position at the National Institute of Mental Health.

June 24, 1970: Mr. Habenicht learned that the NDA for Pondimin had been assigned to Dr. Dorothy Dobbs on June 23 for further review and that Dr. Dobbs has estimated a review of six weeks. Dr. Dobbs is the Director of the FDA's Division of Neuropsychiatric Drugs in the Office of New Drugs. (Now the Office of Scientific Evaluation).

July 6, 1970: The NDA is now in process 383 days since the clock started running after we withdrew the application and re-submitted on June 18, 1969 (see page 6).

MEMORANDUM

FOOD AND DRUG ADMINISTRATION,
Aug. 6, 1970.

To: Dorothy S. Dobbs, M.D., Director, DD 120
From: Martha M. Freeman, M.D., Division of Neuropharmacological Drug Products, BD 120

Requested evaluation of 6 double blind placebo efficacy studies for Fondimine table 20 mg—fenfluramine hydrochloride.

1- *Reginsky* #2050–13—compared fenfluramine 20, 30, 40 mg b.i.d. (*capsule* formulation) vs. placebo in 83 patients on 1000 cal. diet x 12 weeks.

Since capsules rather than tablets were used, the data are not applicable to establish efficacy for the table formulation proposed for marketing. Additionally, deficiencies in study design (lack of detail regarding methods used) preclude scientific evaluation of possible drug effects.

2–6 These 5 investigations were conducted under Master Protocol #25. Four additional studies in this "block" were previously judged by another reviewer to be inadequate to establish efficacy, and have not been included in this review.

The protocol provided for 32 subjects per study subdivided into 4 treatment "cells" of 8 subjects each ("high" and "low" drug—40–60 mg t.i.d. and 20 mg t.i.d.; and "high" and "low" placeebo).

Further subdivision within each "cell" specified 2 male and 2 female subjects per "high" and "low" overweight category (30–75 lbs., and 15–30 lbs., respectively)—thereby providing for 16 sub-groups in each 32 patient study. Precautions to limit non-drug variables included such measures as weight determinations at the same time of day, on the same scale, by the same observer, and similar amount of clothing at each weighing.

Dietary restrictions were purposely omitted in order to demonstrate appetite suppression of sufficient magnitude to result in weight loss from voluntary reduction in calorie intake.