in questions being raised concerning the statistical significance of data submitted. (Additional statistical analyses of our data subsequently convinced us of their significance but was not agreed to by the FDA.)

June 11, 1968: On the invitation of the FDA, representatives of the Company met with the FDA to discuss the design of future controlled clinical studies of fenfluramine vs. placebo to support the effectiveness of this drug. FDA representatives clearly indicated that these studies were absolutely necessary in order to gain NDA approval. (Planning and implementation of these studies was begun immediately. Completion and final analysis of the data would require 17 months.)

June 20, 1968: FDA officially notified the Company by letter that the application was not approvable under Section 505(b)(1) of the act on the basis that the controlled clinical studies revealed deficiencies of the study designs that prevented conclusions concerning the effectiveness of the drug as an appetite suppressant. FDA closed the file.

September 16, 1968: Representatives of the Company and FDA had a conference to discuss the statistical analysis of the clinical data. At this meeting it was agreed that an amended NDA would be submitted with additional statistical treatment of the date in the original NDA and 700 to 800 additional case histories from studies that were still in progress when the NDA was filed.

November 4, 1968: A fourteen volume amendment to the NDA containing over 700 additional case histories was submitted to the FDA. These data included reports on eight controlled studies which were conducted in accordance with presently accepted requirements for satisfactory study design. A revised package insert and a re-analysis of previously submitted data were also included in the NDA amendment.

May 15, 1969: Representatives of the Company met with representatives of the FDA to discuss the status of the NDA. At that meeting the reviewing officer (Dr. Knox) publicly commented that he did not feel that appetite suppressants of any kind were effective. This obvious bias on the part of the reviewing medical officer led to additional discussions with higher officials in the FDA.

June 18, 1969: Since the allotted 180 days allowed for review of New Drug Applications or resubmissions had been exhausted and the NDA had been assigned to a different (and hopefully less biased) medical officer who did not have sufficient time to review the application, the Company withdrew the application and resubmitted it on the same day. A report on a small clinical study was submitted at that time.

In addition to obtaining a less biased review this administrative maneuver had the advantage of keeping the application open and under active review. The alternative would have been receipt of a nonapprovable letter and closing of the application. In that event, the large volume of data submitted on November 4, 1968 would have remained unreviewed until another substantial submission could have been made.

November 25, 1969: The Company submitted an amendment to the application for fenfluramine tablets containing results of a research project by eight different investigators, all of whom evaluated the appetite suppressant effect of the drug according to the same study plan (so-called "block study"). These data and the accompanying statistical analysis confirmed the previous findings that fenfluramine is an effective appetite suppressant and aided patients in weight control programs.

December 11, 1969: At the request of a chemist at the FDA the Company submitted revised bottle labels for use in the event that expiration dating of drug products becomes a requirement prior to the approval of the application. These proposed labels were accompanied by additional stability data on fenfluramine capsules and tablets to support the recommended dating period. It was noted that expiration dating was not a requirement and a disclaimer was included in the Company's letter that this was not a commitment on our part to show expiration dates on the labels of this product unless or until the regulations are revised to require such expiration dating.

January 19, 1970; FDA contacted to determine status of NDA. Only the noncommittal statement that "the medical officer was having discussions with the statisticians" could be obtained. We later learned, however, that the FDA did not as a result of the submission of November 25, 1969, begin another 180-day review period. From this it was concluded that the FDA was desirous of completing the review at an early date.

January 21, 1970: We received a computer print-out from the FDA notifying us that this NDA has been in process 197 days (17 days overdue). No indication of proposed action by the FDA accompanied the print-out.