would be evaluated to determine whether or not the existence of substantial evidence of effectiveness had been demonstrated, and if it had not, procedures would be initiated to withdraw approval of the new drug applications pursuant to section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (e)).

In the same issue of the FEDERAL REGISTER of August 8, 1970 (35 FR 12652), the Commissioner of Food and Drugs issued a Statement of Policy (21 CFR 310.504, formerly 21 CFR 130.46) regarding amphetamine containing drugs, including dextroamphetamine. The order stated that the NAS/NRC had found, inter alia, that this class of drugs had a generally short term (a few weeks) anorectic effect, that there was no evidence that they altered the natural history of obesity, and that they had a significant potential for abuse. The FDA concurred with the NAS/NRC report and, in addition, noted that production data indicated that amphetamines were manufactured and used in quantities greatly in excess of demonstrated medical needs. Accordingly, the order required that such drugs be relabeled to reflect the present state of knowledge concerning amphetamines, their potential for misuse and abuse, and their limited medical usefulness. The order was made specifically applicable to combination drugs which contained dextroamphetamine.

In response to the notice (DESI 5378) of August 8, 1970, Lederle submitted three clinical studies for Bamadex Sequels (Noble, Miller, and Schein) and three clinical studies for Bamadex Tablets (Trodella, Parsons, and Bowlan), together with a list of side effects and combined statistical analysis for all six studies and a combined statistical analysis for the three clinical studies of Bamadex Sequels.

Subsequently, the Commissioner issued a notice of opportunity for hearing, published in the Federal Register of February 12, 1973 (38 FR 4279), covering [redacted] anorectic combinations including Bamadex Tablets and Bamadex Sequels. The notice stated that the submitted data had been reviewed and found not to provide substantial evidence that the drugs were effective as fixed combinations for their claimed uses. Neither, the notice continued, did the submitted data support the contention that the combination products decrease the incidence or severity of side effects or lessen the abuse potential associated with the single anorectic ingredient. Accordingly, the Commissioner proposed to withdraw approval of the named new drug applications and invited holder(s) of new drug applications and other interested persons, including manufacturers and distributors of identical, related, or similar products, to submit on or before March 14, 1973, a written notice requesting an opportunity for hearing. Those requesting a hearing were instructed to state the reasons why approval of the new drug application should not be withdrawn and to provide a well-organized and full factual analysis of the clinical and other investigational data that they were prepared to prove in support of the requested hearing.

In the same issue of the Federal Register of February 12, 1973 (33 FR 4249), the Statement of Policy regarding amphetamines for human use (21 CFR 310.504, formerly 21 CFR 130.46) was revised to reflect that while sufficient data had been submitted (in response to the previous Statement of Policy) to generally support the anorectic efficacy of single entity amphetamine drugs, the degree of extra weight loss was small) a few tenths of a pound a week in many cases), variations were great, and the rate of weight loss decreased after the first weeks of therapy. Accordingly, the Commissioner concluded that single entity oral dosage forms of amphetamine or dextroamphetamine were effective in the management of exogenous obesity as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients in whom obesity is refractory to other measures. The notice advised that anarectic combinations containing sedatives or tranquilizers were regarded as new drugs requiring approved new drug applications and that the data in such applications must meet the requirements of 21 CFR 3.86, fixed combination prescription drugs for human use.

On March 9, 1973, Lederle requested a hearing for NDA 12-570 covering Bamadex Sequels. Lederle did not request a hearing for Bamadex Tablets, and the Commissioner withdrew the approval of the NDA for Bamadex Tablets (NDA 11-280), notice of which was published in the Federal Register of March 30, 1973 (38 FR 8290).

In its hearing request, Lederle contends that its submissions demonstrate (a) that, with respect to weight loss, Bamadex Sequels are significantly better than placebo and not significantly inferior to dextroamphetamine alone, and (b) that the meprobamate component significantly reduces the central nervous system