

evidence suggests that Bamadex is no better than a placebo with respect to the claimed anorectic effect. While the statistical analysis of mean weight losses based on averaging total weight loss over all subjects shows that the difference between Bamadex and placebo was statistically significant, this result is at odds with the investigator's evaluation of the overall clinical response based on number of subjects who lost weight and, in any event, is rendered scientifically unreliable by the study's failure to meet the regulatory criteria for an adequate and well-controlled clinical investigation (21 CFR 314.111(a)(5)(ii)).

Lederle's own investigations and analyses of the Bamadex Sequels studies not only fail to substantiate its rationale for the combination, but affirmatively demonstrate that meprobamate does not reduce the incidence of side effects attributable to the principal ingredient, dextroamphetamine. Moreover, using the clinical response data, only one study (Schein) shows that the difference in anorectic effect between Bamadex and placebo was statistically significant, and in that case the investigator was forced to lower his initial criterion of "satisfactory" to find a statistically significant difference.

B. Bamadex Tablets studies.—Lederle also conducted three clinical studies with Bamadex Tablets (5 mg dextroamphetamine and 400 mg meprobamate). Since both Bamadex Tablets and Bamadex Sequels contain the same active ingredients and are recommended by their respective labels for the same indication, i.e., as a short term adjunct in the treatment of exogenous obesity, and since Lederle in its request for hearing dated March 9, 1973, relied upon a listing of side effects and a combined statistical analysis of data from the three Bamadex Sequels studies and three studies of Bamadex Tablets, the three Bamadex Tablets studies are relevant to Lederle's request for a hearing. With the exception of the dosage schedule (one tablet three times daily), these studies followed the protocol used in the Bamadex Sequels studies. The results are summarized as follows:

1. Parsons, W. B., "Comparative Efficacy of Bamadex Tablets (400 mg meprobamate and 5 mg dextroamphetamine), Bamadex Minus Meprobamate, and Placebo in the Control of Obesity and Measurement of Side Effects," unpublished study, 1971. This study is not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii)(a)(2)(iii) in that it failed to assure that the test and control groups were comparable with respect to the use of drugs other than the test drug. Seventeen of 28 patients in the Bamadex group, 18 of 27 patients in the dextroamphetamine group, and 15 of 29 patients in the placebo group were concurrently using drugs other than the test drug. Concurrent medication included diuretics and tranquilizers which could affect the results of a study designed to measure the anorectic effect and the incidence of adverse reactions related to the central nervous system.

The investigators failed to explain the methods of observation and recording of results with respect to side effects (21 CFR 314.111(a)(5)(ii)(a)(3)). No details are given as to whether subjects were questioned, as to whether they experienced side effects, or whether only the investigators' observations were counted.

This study also fails to provide any statistical analysis of the anorectic data and thus does not comply with 21 CFR 314.111(a)(5)(ii)(a)(5).

Even if the defects above, which render the study not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii), are ignored, the results do not support Lederle's contention that the addition of meprobamate to the combination decreases the incidence or severity of side effects associated with the primary ingredient, dextroamphetamine sulfate.

The results of this study showed a markedly higher occurrence of side effects with Bamadex than with either dextroamphetamine alone or placebo. Of the patients who took Bamadex Tablets, 10 reported side effects while only one in the dextroamphetamine and 4 in the placebo group showed adverse reactions. Since the Bamadex Tablets contain more meprobamate and less dextroamphetamine than the Bamadex Sequels (300 mg meprobamate and 15 mg dextroamphetamine), these results directly contradict Lederle's rationale for the inclusion of meprobamate with dextroamphetamine. If, as the sponsor claims, meprobamate decreases the incidence of adverse effects associated with dextroamphetamine, this decrease should be more evident in the tablet formulation which utilizes a higher ration of meprobamate to dextroamphetamine. As shown above, however, this was not the case. Since there were 10 times as many side effects associated with the use of Bamadex, there is no support whatever for