study methodology; thus, while Dr. Miller was careful to conduct followup weighings at the same time as the initial weighings, neither Dr. Schein nor Dr. Noble did so. Dr. Schein had all his subjects begin the study during the same week; it does not appear that either Dr. Noble or Dr. Miller followed this procedure. It is, therefore, not at all clear that the data from the three studies are sufficiently homogeneous to warrant pooling.

With respect to the combined statistical analysis for all studies, the discrepancies in the tablet studies are even more striking. In the Bowlan study, Lederle reported only one side effect for the Bamadex group whereas the case reports showed seven patients had side effects (No. 401—"nervous," No. 419—"no energy," No. 427—"dry mouth," No. 436—"irritable," No. 442—"increased voiding," No. 449—"emotionally upset," and No. 468—"constipated"). Similarly, while Lederle included only 21 patients in the dextroamphetamine group and 20 patients in each of the Bamadex and placebo groups, FDA's check of the case reports showed that the following patients returned for at least one visit after the initial interview and should have been included in the calculation; the Bamadex group, 30 patients; the dextroamphetamine group, 28 patients; and the placebo group, 28 patients. In studying side effects, it is essential to use all data available. To exclude patients who had only one followup and/or who were dropped from the study is to eliminate from consideration the very patients who may have discontinued because of side effects.

In the Trodella study, Lederle reported three, one and two side effects respectively for the Bamadex, dextroamphenamine and placebo groups while the report forms submitted by the investigator showed the Bamadex group had seven side effects (Nos. 508, 510, 522, and 539—"fatigue," No. 545—"irritable," No. 568—"rash and swelling," and No. 576—"marked increase in blood pressure and headaches"); the dextroamphetamine group, four (No. 507—"constipation," No. 521—"swelling of feet." No. 529—"falls asleep," No. 594—"trouble sleeping if took all three pills"; and the placebo, four (No. 525—"headaches," No. 533—"nauseated and upset," No. 540—"very tired," and No. 590—"sleepy").

Finally, in the Parsons study Lederle based its calculations on 26 patients in the Bamadex and dextroamphetamine gorups and 25 patients in the placebo group. A check of the patient report forms, however, shows that 27 patients should have been evaluated in the Bamadex group (only No. 610 failed to show up after initial visit), 28 in the dextroamphetamine group (all patients evaluated through at least first phase), and 28 in the placebo group (only No. 648 failed to show up after initial visit).

Using Lederle's interpretation in the patient report forms, the results for all six studies show that the identical number of side effects (28) occurred for both the Bamadex and dextroamphetamine groups. There is no basis for the contention that meprobamate significantly reduces the number of side effects associated with dextroamphetmine. In addition, Lederle's statistical analysis of the reduction in the total number of side effects of Bamadex when compared to the total number of side effects for dextroamphetamine only "approached significance."

These data provide no evidence that meprobamate contributes to the combination's claimed effect. Lederle has clearly failed to come forward with any evidence derived from adequate and well-controlled studies showing that meprobamate reduces the number of side effects attributable to dextroamphetamine within the meaning of, and as required by, 21 CFR 3.86(a)(1).

It is also important to note that with respect to the claimed anorectic effect, the primary indication for Bamadex, all individual studies failed to show that the differences between the Bamadex and placebo groups for the 9-week study were statistically significant. Similarly, two of the three tablet studies also failed to show that Bamadex was any better than a placebo.

Since, as shown above, the studies upon which both of the analyses are based are not adequate and well-controlled within the meaning of 21 CFR 314.111(a)(5)(ii), and since the analyses themselves incorrectly and inaccurately report results from the studies, any data from the combined statistical analyses would be scientifically meaningless.

IV. Summary

For the foregoing reasons, the medical evidence submitted by Lederle fails to meet either the statutory standard, section 505(d) of the act (21 U.S.C. 355(d)), for "adequate and well-controlled investigations" as set forth by 21 CFR 314.111(a)(5)(ii) or the requirements established in 21 CFR 3.86 for a fixed combination prescription drug for human use.