

groups were comparable with respect to age, sex, percent overweight distribution, and the mean dosage duration, no such analysis was performed with respect to the use of concomitant medication. This is always a pertinent variable and particularly so in this study where patients were taking diuretics (which could interfere with the effect of test medication on weight loss) and major tranquilizers, analgesics, and antihistamines with sedative effects (which could interfere with adverse reactions related to the central nervous system).

The study fails to explain the methods of observation and recording of results with respect to side effects (21 CFR 314.111(a)(5)(ii)(a)(3)). Thus, no details are given as to whether subjects were questioned as to whether they experienced side effects or whether only the investigator's observations were counted. If the subjects were questioned regarding side effects, no details are given as to the nature of the questions asked. Were the questions only designed to elicit dextroamphetamine-like side effects or were they also directed at uncovering meprobamate-type side effects? Obviously, it makes no sense to claim that the side effects of dextroamphetamine are reduced if the other component, meprobamate, is responsible for equally serious side effects of its own. Without details as to how adverse reaction data were elicited, it is impossible to determine if the investigators took such a possibility into account. Indeed, without any knowledge as to how data were observed and/or recorded, it is impossible to make any meaningful evaluation as to the reliability of the study's findings.

Even if it could be shown that the groups were comparable and that the data had been assembled and recorded in a proper manner, 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. Thus, although the raw data showed that there were numerically slightly fewer side effects associated with patients on Bamadex Sequels (10) than there were with patients who used dextroamphetamine alone (13), Lederle's own statistical analysis demonstrated that this difference was not statistically significant since Lederle stated that the proportion of subjects reporting side effects was not significantly different for the three groups. In other words, there was no assurance that the observed difference was not due to chance. Lederle has failed to show that meprobamate significantly reduces the number of side effects attributable to dextroamphetamine and consequently has failed to demonstrate that meprobamate enhances the safety of the principal ingredient, dextroamphetamine, within the meaning of, and as required by, 21 CFR 3.86(a)(1), and as claimed in its labeling.

The study is incapable of scientifically demonstrating the anorectic effectiveness, or lack thereof, of Bamadex Sequels because, as shown above, the investigator failed to assure group comparability with respect to the use of concurrent medications (21 CFR 314.111(a)(5)(ii)(a)(2)(iii)).

The study also fails to explain the methods of observation and recording of weight loss data (21 CFR 314.111(a)(5)(ii)(a)(3)). Thus the author does not explain whether patients were always weighed at the same time of day, whether the menstrual cycles of female subjects was taken into account and, more importantly, whether any analysis was done to determine which patients, if any, followed their diets. These factors cannot be overlooked in a study designed to measure weight loss.

Using Lederle's criterion for satisfactory weight loss (5 or more pounds in both active drug phases), Lederle's statistical analysis showed that Bamadex Sequels patients did not lose significantly more weight than patients who took the placebo. Lederle also conducted a statistical analysis of the difference in mean weight losses. The difference between the Bamadex and placebo groups were statistically significant only at the end of 3 weeks; there was no statistically significant difference either for the second on-drug period (7 to 9 weeks) or overall (1 to 9 weeks). Thus, Lederle's own findings are inconclusive, and even if they weren't, they would be scientifically meaningless because of the defects pointed out.

2. Schein, M. "A Comparison of Bamadex Sequels, Dextroamphetamine and Placebo on Weight Loss and Number and Types of Side Effects in 90 Overweight Patients," unpublished study, 1971. To exclude climatic conditions as a factor, this investigator had all 90 patients begin the study during the same week. Otherwise, this study followed the same protocol as the just-reviewed Noble study. Accordingly, it too failed to assure comparability with respect to the use of other drugs (21 CFR 314.111(a)(5)(ii)(a)(2)(iii)). Thus, 13 of the 30 patients in the Bamadex group were receiving concomitant medication, while 6 in the amphetamine and 8 in the placebo groups were concurrently using other drugs. As in the