

All three of the clinical studies submitted by Lederle in support of the effectiveness of the sequels shared the same basic defects: They each fail to assure that the test and control groups were comparable with respect to the concurrent use of other drugs, a requirement of 21 CFR 314.111(a)(5)(ii)(a)(2)(iii); and they each failed to explain the method of observation and recording of results (21 CFR 314.111(a)(5)(ii)(a)(3)). These defects conclusively render these submissions inadequate and not well-controlled on their face. As pointed out above, even when these critical defects are ignored, the results, as interpreted by Lederle, of each of the sequel studies taken separately failed to support the contention that meprobamate significantly reduces the incidence of side effects attributable to dextroamphetamine. The combined statistical analyses submitted by Lederle further support this conclusion since Lederle's analysts were unable to conclude that meprobamate reduced the number of side effects in a statistically significant manner (21 CFR 3.86(a)(1)).

None of Lederle's initial statistical analyses for the three sequel studies showed Bamadex to be a significantly better anorectic (overall clinical response) than placebo. Only in the Schein study, when a second analysis was performed and the standard for "satisfactory" clinical response was lowered, did the results show Bamadex Sequels to be significantly better than a placebo. However, these results are not scientifically evaluable since the Schein study is not adequate and well-controlled. Similarly, two of the tablet studies (Parsons and Trodella) also failed to show that Bamadex was significantly better than placebo as an anorectic. While the Bowland study suggests that Bamadex is a significantly better anorectic than placebo, Lederle did not submit any statistical analysis on the anorectic data.

Lederle's statistical analyst, when confronted with the combined data for all three sequel studies concluded that "Bamadex Sequels may have slightly less efficacy in terms of weight loss than dextroamphetamine". Thus, the clinical studies suggest that meprobamate reduces the anorectic effect of dextroamphetamine.

Lederle failed to submit any evidence to support its claim under 21 CFR 3.86(a)(2) in its March 9, 1973 request for hearing that the addition of meprobamate enhances the safety of the principal active ingredient, dextroamphetamine, by lowering its abuse potential.

Finally, although Lederle's current labeling does not claim that Bamadex is safe and effective for the treatment of exogenous obesity with concomitant anxiety and tension, the argument is raised in Lederle's March 9, 1973 request for a hearing and, as stated above, the claim was made in Lederle's earlier Bamadex labeling. However, Lederle has not submitted any evidence to demonstrate the existence of a significant population which fits this description and which requires the dosage of both dextroamphetamine and meprobamate contained in Bamadex for a comparable period of time, as is required by 21 CFR 3.86. To show that such a patient population does exist, it would have been necessary for investigators trained in the use of evaluation of standardized psychological rating scales to have applied the scales to the patient population being studied. Neither investigators with the requisite qualifications nor the rating scales were present in any of these studies.

V. Legal arguments

In its March 9, 1973 request for a hearing, Lederle argues that the three sequels studies demonstrate a statistically significant anorectic superiority of Bamadex Sequels over the placebo and no significant difference from dextroamphetamine. Inasmuch as Bamadex Sequels contains dextroamphetamine, a recognized anorectic, it would not be at all surprising if the data did demonstrate significant superiority for this indication when compared to a placebo. As shown above, however, this is not the case.

Lederle's major argument is that the sequel studies, the list of side effects and the combined statistical analysis, demonstrate that a statistically significant reduction in the central nervous system side effects is achieved by meprobamate, i.e., that meprobamate enhances the safety of the principal active ingredient within the meaning of 21 CFR 3.86(a)(1). As shown above, this contention is not supported by Lederle's evidence. In the first place, none of the submitted studies are adequate and well-controlled clinical investigations within the meaning of section 505(d) of the act (21 U.S.C. 355(d)) and 21 CFR 314.111(a)(5)(ii). Next, even assuming, arguendo, that the studies were adequate and well-controlled, Lederle inaccurately recorded the data from its own patient report