A. *The scientific reliability of the UGDP Study.*—Appendix D of your petition challenges the statistical methodology of the UGDP Study. Other highly qualified experts have defended the UGDP methods and analysis. Their explanations, findings and conclusions are set forth in detail in Appendix A to this response.

Doubtless there are weaknesses in the UGDP Study, as there are in most complex clinical studies. A number of criticisms have been directed at the design and methodology of the Study; these are described and addressed in Appendix A. Despite the merit of some of these and perhaps other criticisms, the UGDP Study presents the best medical evidence available at this time on the cardiovascular hazards of oral hypoglycemic drugs.

Your petition presents only one side of the medical literature on the UGDP Study. We have attached to Appendix A additional articles and editorials which strongly support the reliability of the UGDP Study and reject the conclusion that it should not be given serious consideration. The AMA Council on Drugs has stated:

"Although some flaws exist in the UGDP study it clearly demonstrates that every effort should be made by the physician to control the symptomatic maturity-onset diabetic with diet alone. Should this fail, treatment with insulin oral hypoglycemic agents should be undertaken. If oral hypoglycemic agents are selected for therapy, the results of the UGDP study should be kept in mind. Therefore, the consideration of treatment with oral hypoglycemic agents should be secondary to the use of insulin."

The Ad Hoc Editorial and Advisory Committee on the American Diabetes Association has similarly concluded that:

"In adult onset diabetes with hyperglycemia and glycosuria, symptomatic or not, and in the absence of a ketosis a trial with an appropriate diet should come first. If this does not establish satisfactory control insulin is to be preferred to other therapeutic agents because it is more uniformly effective in controlling hyperglycemia and the UGDP study indicated that it may be safer."

Your petition states that the results of the UGDP Study are not available and therefore not subject to the usual critcial review. We have been assured that the UGDP personnel will honor any reasonable request for data and information.

Finally, you state that FDA acted against the advice of its own advisory committee in accepting the results of the UGDP Study. A review of the minutes of the ad hoc committee convened to discuss this subject in May 1970 indicates that this was not the situation. A copy of those minutes is also attached to Appendix A.

In short, we see no basis for ignoring the findings of the UGDP Study. They must be given very serious consideration by the Food and Drug Administration and the medical profession.

B. *The weight accorded to the UGDP and other studies.*—There now exists substantial evidence of the safety and effectiveness of three different treatment methods for adult-onset diabetes: (1) diet and reduction of excess weight, (2) diet plus insulin, or (3) diet plus oral agents.

From the standpoint of safety, there is overwhelming evidence that diet and reduction of excess weight is preferable to any form of drug therapy. It is well known that drugs have side effects, and that insulin and the oral hypoglycemic drugs clearly produce side effects not attributable to diet alone.

Where diet alone is not adequate to control diabetes, a choice must then be made between insulin and the oral agents. Although the UGDP Study constitutes strong evidence that insulin is safer than the oral agents, because of a lower incidence of cardiovascular death, it cannot yet be said that this has been proven conclusively.

Your petition appended reports by Keen et al., and Paasikivi, presumably to indicate no cardiovascular danger from prolonged tolbutamide therapy. Careful review of these reports reveals that they cannot be considered comparable to the UGDP Study, and thus that they are insufficient evidence to negate the findings of the UGDP Study. (A discussion of these studies may be found on pp. 19 and 19a of Appendix A.) Nor are we aware of any other existing data that justify rejection of the findings of the UGDP Study.

C. *The product labeling required to reflect the available evidence on the safety and effectiveness of diabetic treatment methods.*—As a result of our analysis of the available data, we are requiring product labeling to reflect the following information.

Indications: Oral hypoglycemic drugs are indicated in the treatment of adult-onset, non-ketotic diabetes mellitus only when the condition cannot be controlled adequately by diet and reduction of excess weight alone.