

the shortcomings do not invalidate the central finding that there appears to be an increased risk of cardiovascular mortality associated with the administration of tolbutamide and of phenformin to maturity-onset diabetic patients, compared to treatment with diet alone or diet plus insulin. This conclusion has in the past been reached independently by the UGDP investigators, the FDA, and the Biometrics Society committee, and is again affirmed by the Commissioner. Other clinical trials of these oral hypoglycemic drugs are not comparable to the UGDP study and provide insufficient evidence to negate the findings of the UGDP study.

Accordingly, although comments concerning the validity of the UGDP study and its conclusion will be accepted, comments on this issue that contribute no new information and only reiterate published criticisms, which have already been extensively reviewed by the Food and Drug Administration, are not considered useful at this time.

The Commissioner proposes that a boxed warning concerning the possible increased risk of cardiovascular mortality be included in the labeling for these drugs. This warning is based on the findings of the UGDP study. The Commissioner emphasizes that the requirement for such a warning does not depend upon an absolute certainty that the findings of the UGDP study are correct. Prudence dictates that