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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Oral Hypoglycemic Drugs

SUMMARY AND ANALYSIS

SELECT COMMITTEE ON SMALL BUSINESS
UNITED STATES SENATE
SUBCOMMITTEE ON MONOPOLY AND ANTICOMPETITIVE ACTIVITIES

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A SUMMARY ANALYSIS AND DISCUSSION OF ISSUES HIGHLIGHTED DURING THE 1974–75 HEARINGS ON ORAL HYPOGLYCEMIC DRUGS (COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY, PARTS 25 AND 28), WITH A REVIEW OF CURRENT FINDINGS AND SUBSEQUENT FEDERAL GOVERNMENT ACTIONS RELATING TO THESE DRUGS

NOVEMBER 30, 1978

Printed for the use of the Select Committee on Small Business

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LETTER OF SUBMITTAL

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November 15, 1978

Honorable Gaylord Nelson
Chairman, Subcommittee on Monopoly and
Anticompetitive Activities
Senate Select Committee on Small Business
United States Senate
Washington, D.C. 20510

Dear Senator Nelson:

I am pleased to submit this analysis and review of the oral hypoglycemic drug hearings that were conducted before your subcommittee in 1974-1975. This summary report, prepared at your request, is particularly timely in light of recent re-evaluations of the University Group Diabetes Program (UGDP) studies.

The hearings summary was prepared by Ms. Stephanie Forbes, a private consultant, under a Congressional Research Service contract (CRS 78-62-3). It was reviewed and edited by Ms. Vikki Zegel, Analyst in Life Sciences, of the CRS Science Policy Research Division. The report provides an analytical review of testimony presented during the 1974 and 1975 hearings, as well as an update of what has been learned since those hearings with regard to the risks and benefits associated with the use of oral hypoglycemic drugs by diabetes patients. Recent Federal Government actions relating to these drugs are also highlighted.

May I express my appreciation for this opportunity, on the part of the Congressional Research Service, to cooperate with your subcommittee in the preparation of this timely and most useful report.

Sincerely,

Gilbert Gude
Director

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COMPETITIVE PROBLEMS IN THE DRUG INDUSTRY

Oral Hypoglycemic Drugs

I. INTRODUCTION

A. Purpose

The purpose of this report is three-fold: (1) to review the major issues raised during the Subcommittee's 1974 and 1975 hearings on oral hypoglycemic agents; 1/ (2) to examine these and related issues in the light of current information on these drugs; and (3) to discuss Federal government actions relating to the marketing and labeling requirements for oral hypoglycemic agents.

B. Background

In 1974 and 1975 the Subcommittee on Monopoly of the Select Committee on Small Business heard testimony on the safety, efficacy, and use of oral hypoglycemic agents. 2/ This testimony forms part of the Subcommittee's continuing series of hearings on competitive problems in the drug industry. Expert witnesses from the medical and scientific communities were called to "sort out and analyze what scientific information we have about these drugs and the implications for medical practice." 3/ In his opening statement

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1/ U.S. Congress. Senate. Select Committee on Small Business. Subcommittee on Monopoly. Competitive Problems in the Drug Industry. Hearings, 93rd Congress, 2nd Session and 94th Congress, 1st Session on the Present Status of Competition in the Pharmaceutical Industry: ORAL HYPOGLYCEMIC DRUGS (Volumes 25 and 28). Hearings held September 18, 19, and 20, 1974; January 31, July 9 and 10, 1975. Washington, U.S. Govt. Print. Off., 1974 (pages 10759-11636) and 1975 (pages 13257-13718). [Hereinafter referred to as The 1974-1975 Oral Hypoglycemic Drugs Hearings.]

2/ There are two classes of oral hypoglycemic agents: sulfonylureas and biguanides. The sulfonylureas that have been approved for use in this country include tolbutamide, chlorpropamide, acetohexamide, and tolazamide. At the time of the hearings, the one biguanide approved for use in the United States was phenformin hydrochloride.

3/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10760.

Subcommittee Chairman Senator Gaylord Nelson noted,

> The aims of these hearings are to present for the general public's benefit the best and most objective information available about these drugs. First, whether they are as safe and effective as the medical profession and the public have been led to believe, and second, whether physicians who prescribe them may have sufficient information to weight (sic) the benefits against the risks. 4/

Diabetes mellitus is a metabolic disorder characterized by elevated blood sugar. Symptoms, which may or may not appear in uncontrolled diabetes, include increased thirst, appetite, and urination; weight loss; infections; nerve involvement; and cataracts and other eye disorders. In severe cases of diabetes in which the circulation is impaired, ulcers and gangrene can occur in the feet. Diabetes mellitus, whether mild or severe, is associated with an increased morbidity and mortality due to atherosclerotic complications. Diabetics are more likely than nondiabetics to develop peripheral vascular disease, heart attacks, and stroke.

Diabetes can develop in children and young adults or in older individuals. The former condition, called juvenile-onset diabetes, is usually abrupt and symptomatic and often involves a failure of the pancreatic islet cells to produce insulin. The latter, called maturity-onset or adult-onset diabetes, is often insidious in its development and is frequently asymptomatic.

It has been estimated that there are between 4-1/2 and 5 million diabetics in the United States. Of that number, some 1-1/2 to 2 million use oral hypoglycemic agents at an annual cost of approximately $100 million. 5/

4/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10760.

5/ Ibid., pp. 10860, 10997.

Early experience with the oral agents showed that they are useless in juvenile diabetes, so they are prescribed only for patients with the adult-onset form of the disease. This report, then, is concerned only with oral hypoglycemic drugs in relation to maturity-onset diabetes.

Testimony throughout the hearings focused primarily on the research protocol, statistical analyses, and results of a major prospective clinical trial designed to evaluate the long-term consequences of diabetes mellitus. This study, sponsored by the National Institute of Arthritis, Metabolism, and Digestive Diseases, was begun in 1961 by the University Group Diabetes Program, known simply as the UGDP. The UGDP's original goal was never fully realized; in 1969 the researchers were faced with what appeared to be an excess cardiovascular mortality among patients in the tolbutamide treatment group, and they agreed that the use of this sulfonylurea compound should be stopped. The same decision was made for the biguanide drug phenformin hydrochloride in 1971 when it too appeared to be related to excess mortality. Data gathered up to that point suggested that the oral agents might be no more effective than diet alone or diet plus insulin in managing the mild, adult-onset diabetic who is not dependent upon insulin to remain free of symptoms. While these results were not conclusive, the researchers felt it unethical to continue using potentially toxic drugs that appeared to have little value other than convenience. 6/ With the research on tolbutamide and phenformin stopped in this early stage, there could be no clear-cut, incontrovertible evidence of the oral agents' risks or benefits. Herein lies the origin of what has become known as the UGDP controversy.

6/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10763, 13656.

Of the 21 scientific witnesses called to testify, only two disagreed with the conclusions of the UGDP. The first of these, Dr. Robert F. Bradley, Director of the Joslin Clinic in Boston, noted that he alone of the witnesses then present was critical of the UGDP, and he charged the panel with bias. Senator Nelson explained to Dr. Bradley,

> I am saying there is a standing invitation to the drug companies who manufacture drugs, and who have an economic interest in their use to name anybody. I assume they know the field and are intelligent enough to suggest qualified scientists who are not associated with them at all who have a different viewpoint from the UGDP study, and in each hearing we almost invariably announce--we have announced from the beginning that any time any company's drug is being discussed before the committee, they may suggest witnesses to be heard.
> .....
> I assume that they believe in their drugs and I assume that they would want to recommend some witnesses that take a contrary view. If they do not, it rather surprises me, but that is their problem and not mine. 7/

The second critical witness, Dr. Holbrooke S. Seltzer of the VA Hospital and University of Texas at Dallas commented that "my name might be Daniel under the present circumstance, in the lion's den." 8/ Both Drs. Bradley and Seltzer argued that the UGDP study's randomization process had broken down and that the baseline characteristics of the different treatment groups were not comparable, thus invalidating the study's conclusions.

While cardiovascular mortality and the validity of the UGDP study were the major topics of testimony, witnesses also discussed the possible

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7/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10825, 10826.

8/ Ibid., p. 10880.

hazards of lactic acidosis, hypoglycemia, and weight gain caused by oral hypoglycemic agents. The usefulness of controlling blood sugar in preventing the long-term consequences of diabetes and the loss of effectiveness of the oral agents after a few years of continuous use were also considered.

A few witnesses noted that oral hypoglycemic agents have wide ranging chemical effects quite apart from their action on blood sugar. 9/ In a journal article submitted for the hearings record, 10/ Dr. John K. Davidson of Grady Memorial Hospital listed some of the sulfonylureas' other effects, including "hypothyroidism, skin rashes and photosensitivity, corneal opacities, blood dyscrasias, increased fibrinolytic activity, hyponatremia, water retention, jaundice, liver-enzyme inhibition, heart effects (including inotropism, increased oxygen need, and microgranulomas), elevated blood pressure, altered electroencephalogram in epilepsy, and increased stomach-acid secretion." 11/ Phenformin, Dr. Davidson wrote, "increases anaerobic glycolysis and lactate production and may produce lactic acidosis; it increases blood pressure, heart rate, and need for digitalis; and it decreases gluconeogenesis and glucose absorption." 12/

9/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10762, 10772, 13328, 13535.

10/ Davidson, John K. The FDA and Hypoglycemic Drugs. Journal of the American Medical Association, May 26, 1975: 853-855.

11/ Ibid., p. 853.

12/ Ibid., p. 854.

All of the witnesses agreed that oral hypoglycemic drugs are widely overprescribed and that considerable physician and patient education are necessary to correct this problem. 13/ Witnesses also concluded that some form of new labeling for these drugs was needed. They did not agree, however, on what the contents of that label should be. None of the witnesses from the private sector seemed completely satisfied with the label proposed by the Food and Drug Administration. 14/

Today, scientists still cannot say for certain that oral hypoglycemic drug therapy does or does not carry with it an increased risk of dying from cardiovascular causes. Clearly there have been no major prospective clinical trials published since 1975 to rival the UGDP study in design, extent, and funding. Without such studies it is very difficult to resolve this question. Retrospective studies have been reported, some of which support and some belie the conclusions of the UGDP study. 15/ 16/ 17/ Retrospective studies, however, present problems in interpretation because the treatment groups may

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13/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10835, 10836, 10998, 13307, 13310, 13311, 13319, 13320, 13321, 13656.

14/ Oral Hypoglycemic Drugs, Proposed Labeling Requirements and Public Hearing. Federal Register, v. 40, no. 130, July 7, 1975: 28587-28595. [Hereinafter referred to as The Federal Register Statement, July 7, 1975. See also Appendix C].

15/ Raheja, B.S. Letter: Hypoglycemic Agents in Diabetes Mellitus. Lancet, Feb. 28, 1976: 495.

16/ Coronary Drug Project Research Group, Baltimore. The Prognostic Importance of Plasma Glucose Levels and the Use of Oral Hypoglycemic Drugs After Myocardial Infarction in Men. Diabetes, May, 1977: 453-465.

17/ Krolewski, A.S., et al. The Fates of Diabetic Patients -- Warsaw Epidemiological Study II: Mortality from Coronary Heart Disease Among Diabetics in Relation to Methods of Hypoglycemic Treatment. Acta Medica Polona, v. 18, 1977: 213-230.

not be comparable, the treatments are not randomly allocated, and there is no control group against which the treatment groups can be evaluated. Similarly, with no long-term prospective studies available, the question of how effective the oral agents are in preventing or delaying the long-term consequences of diabetes remains unresolved.

The Federal Government has taken three major steps since the 1975 hearings. The first of these, following close upon the July sessions, was a formal hearing on FDA's proposed label for all oral hypoglycemic agents. During that hearing, critics of the UGDP charged Dr. Christian R. Klimt, the director of the UGDP Coordinating Center, with a conflict of interests because of his association with the phenformin manufacturer U.S. Vitamin. These critics suggested that the data gathered in the clinics might not have been honestly and accurately recorded and reported from the Coordinating Center.

These allegations and the continued controversy over the UGDP and its conclusions led to the Government's second major step: an audit, carried out by the Food and Drug Administration, of the study's raw data. The decision to audit, ordered in December, 1975, was welcomed by both the Committee for the Care of the Diabetic, a group of diabetologists outspoken in its criticism of the UGDP, and Dr. Klimt who had himself requested the audit. This review of the study's raw data, intended as a final effort to end the controversy over the UGDP, has not yet been completed although a final report is expected soon. When the audit is completed, the FDA will decide if new labeling is required for the oral hypoglycemic drugs.

The third major action came on July 25, 1977 when HEW Secretary Joseph A. Califano, Jr. ordered that phenformin hydrochloride be removed from the

market. The order became effective on October 23, 1977 after a 90-day transition period provided so that physicians could re-evaluate their patients taking phenformin and switch them to alternative therapies.

Secretary Califano's order, issued under the "imminent hazard" provision of the Federal Food, Drug, and Cosmetic Act, was based on evidence "that phenformin is associated with lactic acidosis, an uncommon but serious side effect in perhaps as many as 4 per 1,000 users of the drug each year." 18/ About half of the patients who develop lactic acidosis die from it, a risk which the Secretary considered unacceptable when compared to phenformin's disputed benefits.

C. Policy Issues

Several important policy issues were raised during the course of the hearings. These included physician and patient education; informed consent; safety and efficacy; labeling information; and the ethics of drug testing with human subjects.

Witnesses generally agreed that physicians need more education to enable them to critically evaluate the scientific literature and to translate research results into improved clinical practice. 19/ Physicians and patients alike, the witnesses felt, need more dietary education since dietary management is central to the treatment of maturity-onset diabetes.

It was also agreed that patients should take a more active part in their own health care. Patients should be better informed about the potential risks and benefits of each available treatment to enable them to make

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18/ HEW NEWS Release, P77-41, Oct. 22, 1977: 2p.

19/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10802.

reasoned judgements about how their disease might best be treated.

The issue of safety and efficacy was raised several times and posed a difficult problem throughout the hearings. If efficacy means the ability to prevent or delay the long-term consequences of diabetes, then the oral hypoglycemic agents are probably not efficacious. By that reasoning, however, insulin could not be considered efficacious either. The oral agents are effective in lowering blood sugar, thus relieving the immediate and irritating symptoms of diabetes, symptoms such as itching, frequent urination, dehydration, weakness, and leg cramps. Not all mild diabetics have symptoms, however, and it has been argued that asymptomatic patients should not receive oral agents at all. 20/ Even the beneficial effects of the oral hypoglycemic agents may disappear after several years of therapy, a condition termed "secondary failure." 21/

In addition the hearings considered the need for new labeling for oral hypoglycemic drugs. Critics of the UGDP felt that the FDA had a legal obligation to provide both sides of the scientific controversy, a so-called balanced label, on the package insert. FDA representative Dr. Alexander M. Schmidt testified that "if scientific data exist to support a warning, the warning must be presented in unambiguous terms without disclaimers or qualifications that would undermine or destroy its usefulness." 22/ Many of the witnesses questioned the effectiveness of any label on a package insert seen not by patients and physicians but only by pharmacists.

20/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10898, 13295, 13333.

21/ Ibid., p. 10898.

22/ Ibid., pp. 13299-13300.

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A final issue was one of the ethics of drug testing in human subjects. Many witnesses felt that further studies like the UGDP should be conducted to clear up any controversy about the hazards of currently available oral agents and to decide the fate of the new second generation hypoglycemic drugs not yet on the market. Such studies may not, however, be ethical in the light of considerable evidence and the belief of many scientists that these drugs really do carry an increased risk of cardiovascular mortality. Staff economist Benjamin Gordon questioned Dr. G. Donald Whedon of the National Institute of Arthritis, Metabolism, and Digestive Diseases on this issue.

> MR. GORDON. May I ask a question at this point?
> You say that the UGDP investigation stopped using both tolbutamide and phenformin because of their lack of effectiveness and existence of risk.
> Do you think it would be ethical to conduct any more human trials using these drugs?
>
> DR. WHEDON. That is a question that has occurred to us several times and we do not really have an answer to that. It is a very debatable point as to whether we should conduct further trials. I really feel reluctant to give the answer as a single individual. I would think it would take a group of experts who are very knowledgeable of all of the fine points and nuances and the details of the proper aspects of the study of human subjects in relation to disease, to make that decision, but you raise a point of doubt which I think is pertinent. 23/

23/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10859.

II. THE UGDP AND ORAL HYPOGLYCEMIC DRUGS CONTROVERSY

A. History

The bulk of the 1974-1975 hearings was taken up with testimony on the long-term prospective clinical trial conducted by the University Group Diabetes Program, and the legal and scientific controversy which followed the group's first publication in 1970. 24/ The study was initially designed to answer a question long-standing in the field of diabetology: does the strict control of blood sugar level prevent or ameliorate the long-term vascular complications of diabetes mellitus? These complications involve the small vessels of the eye and kidney, the larger vessels of the heart, and the peripheral blood vessels; they can lead to blindness, kidney damage, myocardial infarction, and gangrene. Since the advent of insulin and the prolongation of life among diabetics, these long-term complications have become the real problem in diabetes.

The UGDP study was begun in 1961 with the financial support, estimated at $7.3 million at the time of the hearings, 25/ of the National Institute of Arthritis, Metabolism, and Digestive Diseases. The Institute was particularly interested in "evaluating the long term effects of using a noncurative chemical in the treatment of a chronic disease." 26/ The Food and Drug Administration's approval of oral hypoglycemic agents meant only that no short-term harmful side effects had been discovered.

24/ The University Group Diabetes Program. A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. I. Design, Methods and Baseline Results. II. Mortality Results. Diabetes, v. 19 (suppl. 2), 1970: 747-830.

25/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10803.

26/ Ibid., p. 10762.

Twelve university medical centers and 1,027 diabetics were involved in the study. Patients selected for the program were maturity-onset diabetics who had been diagnosed no more than a year before entering the study and who did not require insulin to remain free of symptoms.

All of the patients were given appropriate diabetic diets and randomly assigned to one of four treatment groups: (1) fixed dose of tolbutamide; (2) fixed dose of insulin; (3) variable dose of insulin adjusted as necessary to control blood glucose level; or (4) placebo, given to control for any subjective effects a patient might derive from the mere act of taking some medication. In effect, the placebo group represented diabetes therapy using diet alone. Eighteen months after the study began a fifth treatment group was added in which a fixed dose of phenformin hydrochloride was used.

In 1969 the study took an unexpected turn; it appeared that more patients were dying from cardiovascular causes in the tolbutamide group than in the diet or insulin groups. Far from preventing vascular complications, tolbutamide seemed to be making them worse. After a great deal of discussion and data evaluation, the investigators decided to discontinue tolbutamide treatment since the drug's possible toxicity did not appear to be outweighed by potential benefits. Dr. Max Miller, Chairman of the UGDP, recalled these events in his 1974 testimony:

> ...it became clear that those patients in the tolbutamide group were suffering from an increased mortality rate compared to the other three treatment groups, placebo and the two insulin groups. This trend was monitored carefully, and as the differences approached statistical significance, outside statistical consultants were invited to review and assess all the available data. These discussions went on for approximately 9 months before the final decision was made to discontinue the use of tolbutamide in the study. It was clear that the decision was made to a large extent on the rules laid down in the Kefauver amendment to the

Food and Drug Laws in the early sixties which was passed as a result of the thalidomide disaster. This simply stated that drugs should be used by the public only if the benefits exceeded the risks, and that this evaluation should be made on the basis of scientific studies rather than anecdotal clinical reports or impressions. For this reason we could not in all good conscience continue to treat patients in the study with oral agents until a larger excess of deaths developed. 27/

The UGDP officially reported its findings to the Food and Drug Administration which, after reviewing the study, issued a statement in support of the group's conclusions. The statement, released to the press on May 22, 1970, indicated that relabeling for the oral hypoglycemic drugs was in order. In October, 1970 the FDA distributed a Current Drug Information Bulletin to all health professionals confirming its agreement with the UGDP and recommending that the sulfonylureas be prescribed only for "symptomatic adult-onset, nonketotic diabetics who cannot be adequately controlled by diet or weight loss alone and in whom the addition of insulin is impractical or unacceptable." 28/ Essentially the same recommendation was made by the American Diabetes Association in November, 1970 in an editorial accompanying the UGDP's first published report. The American Medical Association Council on Drugs published a similar statement in the same supplement to Diabetes that year. 29/

27/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10762-10763.

28/ The Federal Register Statement, July 7, 1975, p. 28588 [See Appendix C].

29/ AMA Council on Drugs. Statement Regarding the University Group Diabetes Program (UGDP) Study. Diabetes, v. 19 (suppl. 2), 1970: vi-vii.

In May, 1970 the UGDP investigators also discontinued the use of phenformin hydrochloride. This time it appeared that the excess mortality was not limited to cardiovascular causes. This trend appeared in the second rather than the third year of use as had been the case with tolbutamide. Phenformin was, apparently, a more toxic drug. Dr. Christian R. Klimt, a UGDP participant, stated during the hearings that "The increased mortality in the phenformin-treated group appeared very early in the study and was already visible in the data of the second year." 30/ In later testimony, Dr. John K. Davidson, who was instrumental in changing the standard diabetes therapy at Grady Memorial Hospital, commented that "phenformin therapy was associated with a significantly increased total and cardiovascular mortality, and I would like to return to this, because we have been talking almost entirely about tolbutamide when we are also dealing with phenformin, which is in fact a more toxic drug than tolbutamide is." 31/

In June, 1971 the FDA issued a Drug Bulletin outlining proposed changes in the labeling for all sulfonylurea drugs and reiterating its past recommendations for their use. The new labeling was challenged in October by the Committee for the Care of the Diabetic, a group of physicians who criticized the UGDP and opposed new labeling for oral hypoglycemic agents. The still active committee, which includes some of the country's leading diabetologists, petitioned the Commissioner to rescind his position, maintaining that the UGDP study was an improper basis for the agency's decision. The committee cited other studies which, it believed, demonstrated the safety of oral hypoglycemic therapy and insisted that any labeling for these drugs should reflect both sides of the scientific controversy.

30/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10776.

31/ Ibid., p. 10839.

After reviewing the committee's material and answering each of its criticisms, the Commissioner decided to stand by the agency's original position, stating that "an undiluted and unencumbered warning in the labeling of oral hypoglycemic drugs regarding cardiovascular hazards was fully warranted by the available evidence." 32/ The agency's position was restated and extended to include the biguanides in an FDA Drug Bulletin issued in May 1972 and printed in the hearings record. 33/

The Committee for the Care of the Diabetic then requested a formal evidentiary hearing before the agency. When its request was denied, the committee filed suit in the United States District Court of the District of Massachusetts asking that the Food and Drug Administration be enjoined from requiring manufacturers to include a warning of associated cardiovascular hazards in their labeling for oral hypoglycemic drugs. In November, 1972 the FDA was enjoined from implementing the proposed labeling requirement. The injunction was vacated by the U.S. Court of Appeals which remanded the case to the FDA for further consideration.

In the meantime, the National Institute of Arthritis, Metabolism, and Digestive Diseases sought an independent review of the UGDP study's design and statistical analyses in an attempt to end the controversy. A contract was awarded in 1972 to the Biometrics Society, an international organization of biostaticians. The six-member committee chosen to undertake the review conducted an in-depth assessment of the design, conduct, and analysis of the UGDP and similar controlled trials involving oral hypoglycemic agents. 34/

32/ The Federal Register Statement, July 7, 1975, p. 28588 [See Appendix C].

33/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10966 [See also Appendix D].

34/ Biometrics Society Review Committee members are listed in Appendix I.

In the final section of its report, published in 1975 and printed in full as an Appendix to the 1975 hearings, the committee concluded that while some reservations about the toxicity of oral hypoglycemic drugs remained, the evidence of their harmfulness was moderately strong. Furthermore, the committee felt that the proponents of these drugs still had to prove their case with scientifically adequate studies. 35/

With the Biometric Society review completed and favorable to the UGDP and its conclusions, the FDA reissued proposed labeling requirements for hypoglycemic agents and held further hearings. 36/ The agency hoped that by following, once again, the formal rulemaking procedure, it would strengthen its position and avoid further litigation. 37/ Far from being resolved, however, the controversy spilled over into these hearings with charges of conflict of interests and data tampering. The result was an FDA audit, ordered in December, 1975, of the UGDP study's raw data. That audit has yet to be completed.

35/ Report of the Committee for the Assessment of Biometric Aspects of Controlled Trials of Hypoglycemic Agents. Journal of the American Medical Association, v. 231, 1975: 583-623.

36/ The Federal Register Statement, July 7, 1975 [See Appendix C].

37/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13291.

B. 1974-1975 Hearings

At the heart of the scientific controversy over oral hypoglycemic drugs lies the UGDP study, the significance of which was underscored at the hearings by Dr. Alexander M. Schmidt, who was at that time the Commissioner of the Food and Drug Administration. Dr. Schmidt explained that while other studies may or may not lend support to its findings, "the prospective UGDP study must be accorded far greater weight and is alone a sufficient basis for our proposed actions." 38/ Dr. Schmidt also praised the UGDP study as "an adequate and well-controlled study -- by far the most extensive and best examination of the long-term effects of oral hypoglycemic agents yet ever undertaken." 39/ Dr. Schmidt's sentiments were shared by a number of other witnesses 40/ whose testimony concentrated on the study's design, statistics, results, criticisms, and reviews, often to the exclusion of other scientific studies.

Not all of the scientific community, however, agreed with Dr. Schmidt's assessment of the UGDP study. By the time the hearings began in 1974 the controversy had already been going on for four years and showed no signs of abating. The reasons for the reluctance on the part of some scientists and clinicians to accept the UGDP results appeared to be emotional as well as professional. In his testimony before the Subcommittee,

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38/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13298.

39/ Ibid., p. 13299.

40/ Ibid., pp. 10864, 10901, 11007, 11014, 11126, 11127, 13259, 13267, 13268, 13292, 13666, 13690, 13706.

Dr. Frank Davidoff of the University of Connecticut discussed what he believed to be some of the emotional reasons for the heated dispute generated by the UGDP study.

> In effect the study challenged both safety and effectiveness. Most of the controversy that has reached the public eye has revolved around the safety data, and the effectiveness issue has been in the background. However, I submit that if the oral antidiabetic agents had been known to be uniquely and unequivocally effective in preventing the late complications of the disease, hardening of the arteries, kidney failure, blindness, nerve damage, et cetera, all the devastating complications of the disease, we and our patients would have risked small and perhaps doubtful increases in risk of fatal complications from a heart attack. We make this kind of judgment every day in medicine.
>
> The UGDP study did indeed present the best data so far that the effectiveness of oral antidiabetic agents, or of insulin, for that matter, in preventing the late complications was essentailly nil. And I submit, therefore, that while a challenge to the safety of the oral antidiabetic agents might have been acceptable to the medical profession, a challenge to effectiveness cut us to the quick.
>
> It is perhaps worth noting that in a historical context, that challenges to the effectiveness of therapy have frequently provoked violent reactions in the medical professions. I call to your attention the story of Dr. Codman of Boston who in the first decade of this century proposed that the effectiveness of therapy could be actually measured in terms of outcome, and could be judged by the medical profession. For his ideas he apparently lost his hospital admitting privileges and began his own private hospital and published studies on the effectiveness of intervention in medical care.
>
> The idea of quality control in medicine, measurement of effectiveness, measurement of outcome of therapy, is fortunately now rapidly gaining acceptance, and you are all familiar with the PSRO-type legislation which embodies these principles.

> The general principles of evaluating quality include measurement both of the process of medical therapy, and the outcome, particularly that outcome, the effects of intervention on outcome, and the use of objective studies, both prospective and carefully controlled. Many of these attempts at measuring outcome are now perceived as threatening; in a sense therefore, the UGDP study is a creature of the times, in two senses perhaps. It was an outcome study, and it has been perceived as threatening. 41/

According to Dr. Davidoff, if only the safety of the drugs had been challenged, the controversy might never have exploded. "It is one thing," Dr. Davidoff wrote, "to challenge the safety of a drug: such a challenge would not, in itself have been particularly telling, since, as I have already noted , many drugs have withstood assaults on their safety because they were also highly effective. But to be told that the drugs we have been giving to diabetics for 12 years were unnecessary, beside the point, in a word, ineffective, was, as I see it, a more serious blow to our professional pride." 42/

Many private physicians criticized the UGDP conclusions because, based on their own practices, tolbutamide did not appear to cause an increase in cardiovascular mortality. This criticism was understandable, according to Dr. Schmidt, since an increase in cardiovascular death rate of one percent per year over an expected rate of less than one percent per year "can only be demonstrated by a large well-controlled study." 43/ The increased morality is simply too small to be detected by a private physician with an average practice.

41/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10810-10811.

42/ Ibid., p. 11009.

43/ Ibid., p. 10901.

The major scientific criticisms of the UGDP study were summarized by Professor Colin White in his testimony during the 1975 sessions. Dr. White served as the Chairman of the committee appointed by the Biometrics Society to assess the scientific quality of the UGDP and other controlled trials of oral hypoglycemic agents. These criticisms are:

(1) the excess mortality in the tolbutamide group was due to the data obtained from just a few clinics;

(2) the studies of Keen et al. and of Paasikivi contradict the U.G.D.P.;

(3) the baseline differences among the treatment groups account for the finding of the adverse effects from tolbutamide;

.....

(4) the findings on the effect of tolbutamide are flawed by the failure to adapt dosage to individual need;

(5) the evidence was not adequate to justify the discontinuation of the oral drugs. 44/

After evaluating each of these criticisms the committee concluded in its written report 45/ and stated to the Subcommittee "that it remains with the proponents of the oral agents to conduct scientifically adequate studies to justify the continued use of such agents." 46/

The Biometrics Society report represented a major effort to resolve the controversy over the UGDP and oral hypoglycemic agents. Dr. J. Richard Crout, Director of FDA's Bureau of Drugs, testified, "In our opinion, the review by the Biometric Society was in far greater detail, far greater

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44/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13692.

45/ Reprinted for the hearings record, The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 13337-13377.

46/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13693.

depth, than any of the others, and is again the overriding review of the study." 47/ Dr. Crout also noted that the Biometric Society review was the only third party review; all the other reviews were conducted by individuals who were in some way involved in the controversy.

The Food and Drug Administration's intention of requiring a uniform warning label for all oral hypoglycemic drugs was also criticized. The UGDP study dealt only with tolbutamide and phenformin and, the critics reasoned, there was no scientific justification for extending the study's conclusions about these drugs to all other related compounds. However, it was the FDA's position and Dr. Schmidt testified,

> Our warning also points out that, although only one sulfonylurea and one biguanide were included in the UGDP study, it is prudent from a safety standpoint, in view of the similarities in chemical structure and mode of action of drugs within each of these two categories, to consider that the UGDP findings may apply to the other drugs in each category. The warning has thus been applied to all sulfonylurea drugs, and the one biguanide drug marketed in this country. 48/

Only two scientific witnesses, Drs.Robert F. Bradley and Holbrooke S. Seltzer, offerred direct testimony to the Subcommittee critical of the UGDP study. Dr. Bradley, who is Chairman of the Committee for the Care of the Diabetic, testified that the study's randomization process had broken down and that the baseline distribution of risks was not the same for each treatment group. Simply by chance, he explained, more patients at risk of developing cardiovascular problems were assigned to the tolbutamide group than to the diet or insulin groups. Dr. Bradley also stated that many

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47/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13301.

48/ Ibid., p. 13302.

of the patients could have been diabetics for several years even though they had been diagnosed only a short time before their entry into the study. These two factors, Dr. Bradley testified, render the study results useless. 49/

Dr. Seltzer argued that the UGDP investigators reached their conclusions prematurely. In his written statement he pointed out that "Cardio-vascular mortality levelled off after May, 1968, 15 months before Tolbutamide was stopped." 50/ He wrote that "between October, 1969 and September, 1973 there has been a reversal in the cardio-vascular death rate between the placebo group and the Tolbutamide group." 51/ Dr. Seltzer faulted the UGDP study's protocol because it recorded patients as being in the treatment group in which they were started even when they were switched to a different treatment group later in the program.

> By the terms of the UGDP study protocol itself, all patients who were originally started on Tolbutamide who subsequently died a cardio-vascular death had to be recorded as a Tolbutamide cardio-vascular death, regardless of the fact that he (sic) had previously stopped taking the drug or had switched to another treatment group. 52/

Dr. Seltzer, as did Dr. Bradley, criticized the UGDP study for what he considered "the non-homogeneity of the study population," resulting in "more patients with pre-existing cardio-vascular disease being enrolled in the Tolbutamide treatment group." 53/ Other criticisms of the UGDP,

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49/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10829-10830.

50/ Ibid., p. 11115.

51/ Ibid., p. 11114.

52/ Ibid., p. 11115.

53/ Ibid., p. 11116.

criticisms which essentially reiterate the sentiments of Drs. Bradley and Seltzer, were provided to the Subcommittee by various pharmaceutical companies and printed in the hearings record. 54/

The conclusions of the UGDP study were either unaccepted or misunderstood by the majority of private physicians, judging from the continued widespread use of the oral agents. These drugs had always been overprescribed, a fact upon which UGDP critics and supporters alike agreed. 55/ It was estimated that some 80 to 99 percent of the patients receiving these drugs did not need them. 56/ The UGDP study had seemingly little effect on this vast overprescription. 57/ Dr. Thomas C. Chalmers of Mount Siani Medical Center testified,

> One important point that I would like very much to make, however, is that the UGDP studies and all of these additional bits of evidence have not had any perceptible impact on the practice of medicine in this country, and as a matter of fact, in Canada. 58/

In his written statement, Dr. Chalmers presented a table of data, gathered by the National Disease and Therapeutic Index, on the use of hypoglycemic agents. These data show about a 20 percent drop in tolbutamide sales following the report of the UGDP study. The sales of other oral agents,

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54/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 11540-11624.

55/ Ibid., pp. 10835, 10983, 13307, 13319, 13320, 13321, 13656.

56/ Ibid., p. 13536.

57/ Ibid., pp. 10798, 10799, 10916, 10998, 10999, 11012, 13647, 13657, 13660, 13685.

58/ Ibid., p. 10798.

however, increased almost proportionately. Within two years tolbutamide sales had recovered and were back up to their old rate of increase. Dr. Chalmers commented, "The only possible explanation for the steady increase in the use of oral agents in spite of the fact that they may be killing patients and that they are in the long run largely ineffective in controlling diabetes is that the physicians in general do not believe the UGDP studies." 59/

Three reasons were brought out during the hearings to explain why so few physicians believed the UGDP findings:

(1) the widespread repudiation of the study by a number of respected diabetologists; 60/

(2) lack of physician education in critically evaluating research and then translating research results into clinical practice--the knowledge-performance gap; 61/

(3) the influence of "throw away" medical journals, the revenues for which are gleaned largely from drug advertisements, and detail men from drug companies. 62/

59/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10999.

60/ Ibid., p. 10999.

61/ Ibid., p. 11013.

62/ Ibid., pp. 10999, 13306.

The hearing record contained the following summary of what one Upjohn salesman told a physician about the UGDP study:

> (1) there is no cause-and-effect relationship revealed in the study between the use of Orinase and the incidence of coronary disease; (2) the statistics are so complicated that only a student of statistics can evaluate them; (3) 2-1/2 less coronaries in the study would not change the results; (4) 35 diabetologists do not accept the results of the study; (5) the director of the study in Cincinnati does not accept the results; (6) two other men in the study do not accept the results; (7) Dr. Kent of Cleveland does not accept the results of the study; (8) Cincinnati added patients from its cardiac unit to fill its quota of diabetic patients; (9) most of the coronaries came from two centers; (10) there was no follow-up on five patients in the study; (11) the dose of Orinase was fixed so, therefore, it was not a correct dose for many patients; (12) the Joslin Clinic and other diabetes clinics have reviewed their cases in their clinics, and the result cannot support the results of the university study; and (13) the FDA will probably modify the ruling on Orinase. 63/ 64/

The UGDP study did affect the standard therapy for maturity-onset diabetics in a number of large hospitals. Mentioned during the hearings were the Grady Memorial Hospital, the Columbus, Georgia Medical Center, Cleveland Metropolitan Hospital, and the Mayo Clinic. These hospitals either abandoned the oral agents entirely or greatly curtailed their use after evaluating the UGDP reports. Dr. Davidson of Grady Memorial Hospital and Dr. Palumbo of the Mayo Clinic both testified that their diabetic patients do just as well or better without the oral hypoglycemic drugs as with them. 65/

63/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13306.

64/ Orinase is Upjohn's trade name for tolbutamide.

65/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10840, 13274.

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The critics and proponents of the UGDP study agreed on two points: (1) the study is not perfect and, because the drugs were discontinued before statistical significance was reached, no positive conclusions about toxicity can be made, and (2) the UGDP trial is probably the best study of its kind. Regardless of this or any agreement, the controversy over the UGDP study was carried throughout the hearings and remained unresovled at their adjournment.

C. 1975-1978

Letters and articles both in support of and critical to the UGDP study continue to appear in the scientific literature. In general these articles reiterate statements made during the 1974-1975 hearings. It is interesting that some seven years after the UGDP's first publication, Dr. John N. Fain of Brown University would open a symposium on oral hypoglycemic agents with the statement, "Today, we are in the midst of a somewhat emotional debate over whether we have in fact 'cured them dead' with the oral-antidiabetic drugs." 66/ That emotional debate is still going on in 1978.

During the 1975 FDA hearing on proposed labeling for the oral agents, the controversy was rekindled with a new charge brought by former UGDP participants. These scientists, chief among whom was Dr. Angela J. Bowen, suggested that the data gathered in the clinics might not have been accurately recorded and reported by the data co-ordinating center. 67/ This charge led to an official FDA audit, still in progress, of the study's raw data. The possibility of actual data falsification and fraud was discussed in a recent Medical Tribune article. 68/ Additional material on the UGDP controversy is scheduled for publication in future issues of this medical news sheet.

66/ Fain, John N. Mode of Action of Oral Hypoglycemic Drugs, Introductory Remarks. Federation Proceedings, December, 1977: 2712.

67/ UGDP Official Charged with Conflict of Interest. Medical Tribune, Sept. 17, 1975: 19.

68/ A UGDP 'Frame-Up' of Two Diabetes Drugs is Charged. Medical Tribune, July 5, 1978: 1, 10-11.

Judging from the number of prescriptions still being written for the oral hypoglycemic drugs, the practicing physician still does not accept or does not understand the results of the UGDP study. While the number of prescriptions written for tolbutamide and phenformin declined somewhat after 1975, the number written for the other sulfonylureas did not. 69/ This widespread use of the other sulfonylureas goes on in spite of the facts that the FDA believes the results from tolbutamide studies to be applicable to all related compounds and that it has proposed warning labels for all oral hypoglycemic drugs. 70/ 71/

In the third quarter of 1977, before it was taken off the market, some 429,000 prescriptions, including 84,000 new prescriptions, were written for phenformin hydrochloride. 72/ At that time it was the least prescribed of all the oral agents, and with its ban by Secretary Califano, at least one chapter of the oral hypoglycemics controversy may have come to a close.

69/ Oral Hypoglycemic Drug Certification Data, 1973-1977. As prepared and submitted by the Food and Drug Administration [See Appendix E].

70/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13302.

71/ The Federal Register Statement, July 7, 1975, p. 28858 [See Appendix C].

72/ Oral Hypoglycemic Drug Certification Data, Third Quarter, 1977. As prepared and submitted by the Food and Drug Administration [See Appendix F].

III. CARDIOVASCULAR MORTALITY AND ORAL HYPOGLYCEMIC AGENTS

A. 1974-1975 Hearings

The most provocative and controversial finding of the UGDP study was that patients taking tolbutamide or phenformin hydrochloride have a greater risk of dying from cardiovascular causes--those causes related to the heart and blood vessels--than patients taking insulin or restricted to dietary therapy. Understandably, then, the possibility that these drugs are somehow toxic to the cardiovascular system received a great deal of attention during the hearings. Most of that attention focused on tolbutamide and the other sulfonylureas rather than on phenformin. Dr. Colin White of the Biometrics Society review committee commented on the relative lack of controversy over the phenformin results:

> It is interesting to note that the UGDP presented results on phenformin which are quite comparable to those on tolbutamide: the death rate from cardiovascular causes was approximately the same in the two cases. The findings on phenformin, if one can judge from the absence of criticism, appear to have been accepted by medical scientists, even if they have not so far been translated effectively into medical practice. Yet these findings also were made by the UGDP using the methods that have come under heavy criticism when applied to tolbutamide. 73/

While the UGDP study was considered the most significant piece of evidence for the oral agents' cardiovascular toxicity, 74/ other scientific studies were offered in support of this possibility.

73/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13259.

74/ Ibid., p. 13298.

These studies fall into two categories: (1) basic animal and human studies on the pharmacologic action of the drugs and (2) retrospective studies of human diabetics.

During the 1974 sessions, Dr. Roger F. Palmer of the Department of Pharmacology, University of Miami, discussed the direct action of sulfonylureas on heart tissue. His initial interest in these drugs was part of a departmental interest in inotropic agents--compounds which strengthen the force of the heart's contraction. Dr. Palmer and his colleagues, Drs. Gerald S. Levey and Kenneth C. Lasseter, found that

> tolbutamide had a significant inotropic effect on cat, rabbit and human heart tissue but not on heart tissue from dogs. The general effect that we observed was an increase in the force of contraction of the heart muscle and an increase in spontaneous electrical activity. 75/

In addition, Drs. Lasseter and Levey found that all drugs with a sulfonylurea structure behave in this way to a greater or lesser extent. Dr. Palmer testified that patients taking these drugs might be more prone than other diabetics to cardiac arrhythmias (irregular heart rhythms) since the drugs render heart tissue more excitable. The increased force of contraction induced by these drugs would drive the heart to do more work and therefore to consume more oxygen. These findings were published in 1974. 76/

Dr. Palmer's group also injected therapeutic doses of tolbutamide into humans undergoing cardiac catheterization. The result was an increase

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75/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 11098.

76/ Levey, Gerald S., Kenneth C. Lasseter, and Roger F. Palmer. Sulfonylureas and the Heart. Annual Review of Medicine, v. 25, 1974: 69-74.

in the force of heart contraction, an increase in the blood output from the heart, and a modest rise in blood pressure. These effects, Dr. Palmer explained, "occurred at blood levels of the drug that would be found in patients receiving the drug on a long-term basis." 77/

In his prepared statement Dr. Palmer wrote that he was surprised to find that "drugs such as this which are used in patients with a high risk of cardiovascular disease had not been examined for their effects on heart or blood vessels before their introduction to the public." 78/ He added by way of comment on drug testing procedures in this country that the dog, which was found to be insensitive to the inotropic effects of sulfonylureas, is commonly used to screen drugs prior to Phase I testing in humans.

Dr. Palmer himself raised an important question regarding his research. He asked, "Is an inotropic stimulus caused by the sulfonylureas capable of producing heart disease and death in human beings?" 79/ Dr. Palmer believes it is.

> In my view, because of the increase in contractile force and the increase in excitability, such a conclusion would be inescapable because any time that oxygen consumption and excitability are increased, a greater demand upon the heart is occasioned. Patients at risk are usually

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77/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 11098.

78/ Ibid., p. 11100.

79/ Ibid., p. 11099.

diabetics who have a higher incidence of arteriosclerotic heart disease and who may not be able to respond to the increased demand caused by these sulfonylurea agents. Therefore, one would anticipate that patients at risk from heart disease would have a significantly increased risk of cardiac mordibity and mortality when sulfonylurea agents are used. 80/

Two similar animal studies were discussed by FDA Commissioner Schmidt during the 1975 sessions. One of these studies, conducted by Dr. Robert W. Wissler et al. and supported by the Food and Drug Administration, looked at the chronic effects of tolbutamide in the rhesus monkey. 81/ The researchers found, according to Dr. Schmidt, that "coronary artery lesions were almost two times more frequent and three times more severe in the tolbutamide-treated animals than in the control animals." 82/

The second study, conducted by Dr. C.F. Wu and colleagues at the New Jersey Medical School, examined the effects of tolbutamide on heart function in dogs with chemically-induced diabetes. 83/ These investigators found that animals treated for one year with tolbutamide at "doses which improved glucose tolerance in diabetics," had reduced left ventricular function and altered heart morphology. 84/ It is perhaps significant that

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80/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 11099-11100.

81/ Borensztajn, J., G.S. Getz, S. Glagov, A. Rubenstein, C.H. Ts'ao, and R.W. Wissler. A Study of the Chronic Effects of Tolbutamide in the Rhesus Monkey. FDA No. 72-114, Feb. 15, 1975.

82/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 13704-13705.

83/ Wu, C.F., B. Haider, S.S. Ahmed, H.A. Oldewurtel, M.M. Lyons, and T.J. Regan. Tolbutamide Induced Alteration of Left Ventricular Function in Diabetes. Clinical Research, April, 1975: 215A.

84/ Ibid., p. 215A.

the left ventricle was affected since it is this chamber of the heart which, by the force of its contraction, drives the blood into the aorta and hence to the rest of the body.

Some of the effects of sulfonylureas observed in animal studies were also seen in phenformin users in the UGDP study. These effects, including increased blood pressure and heart rate, were discussed in written and oral testimony before the Subcommittee 85/ and in the UGDP's 1975 published report. 86/ These effects were offered as a possible explanation for the observed increased cardiovascular mortality among phenformin users.

Two retrospective studies were also mentioned to support the UGDP's finding of cardiovascular toxicity. One of these was discussed at the January 31, 1975 session by Dr. P.J. Palumbo of the Mayo Medical School. Dr. Palumbo and his colleagues analyzed data on the incidence, prevalence, and mortality of diabetes mellitus between 1945 and 1970 in Rochester, Minnesota. Their preliminary analysis of data on 1,090 diabetics, 138 of whom were taking oral agents, "contains some hints that survivorship may be lower in diabetics on oral antidiabetic agents," than in those on diet or insulin therapy. 87/ Dr. Palumbo emphasized, as did other witnesses, that while "hints and leads from retrospective studies can be extremely valuable in leading to a new hypothesis...alone they cannot form the basis of any firm conclusions concerning treatment effects." 88/ Dr. Palumbo commented that the UGDP study was the sort

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85/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10766, 11087, 13703.

86/ The University Group Diabetes Program. A Study of the Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. V. Evaluation of Phenformin Therapy. Diabetes, v. 24 (suppl. 1), 1975: 65-184.

87/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13273

88/ Ibid., p. 13688.

of controlled, randomized, clinical trial which allows treatments to be compared and upon which firm conclusions can be made. In his opinion, "another randomized trial study of treatment in diabetes is not ethically justified, as the data from the University Group Diabetes Program clearly indicate an adverse effect of the oral antidiabetic agents on survivorship in the diabetic." 89/

FDA Commissioner Schmidt mentioned another retrospective study of diabetic patients at the Joslin Clinic in Boston. The study is reported in a doctoral thesis by Paula Helene Kanarek, excerpts of which were printed in the hearings record. 90/ According to Dr. Schmidt, certain subgroups of the insulin-treated patients appeared to have better survival rates than tolbutamide-treated patients with comparable glucose abnormalities. Dr. Schmidt emphasized, once again, that retrospective studies are difficult to interpret because treatment groups may not be comparable and treatments are not randomly allocated. 91/

The two studies mentioned most often in opposition to the UGDP study are those of Keen et al. and Paasikivi. 92/ 93/ The Keen study is a prospective, randomized, double-blind investigation, as is the UGDP study.

89/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 13668-13669.

90/ Ibid., pp. 13393-13412.

91/ Ibid., pp. 13703-13704.

92/ Keen, H., R.J. Jarrett, C. Chlouverakis, et al. The Effect of Treatment of Moderate Hyperglycemia on the Incidence of Arterial Disease. Postgraduate Medical Journal, v. 44, 1968: 960-965.

93/ Paasikivi, J. Long-Term Tolbutamide Treatment After Myocardial Infarction. Acta Medica Scandinavia, suppl. 507, 1970: 1-82.

The investigators followed, for up to seven years, 248 mild diabetics who were treated with either tolbutamide or a placebo. A fixed dose of tolbutamide was used, a procedure for which, interestingly enough, the UGDP study was criticized. 94/

The Paasikivi study was a prospective, randomized, single-blind trial involving 178 survivors of first myocardial infarctions. The subjects were treated with a placebo or a fixed dose of tolbutamide. Patients with overt diabetes were excluded from the study. Of the 178 patients participating in the study, 52 were diagnosed as diabetic.

Neither the Keen nor the Paasikivi studies showed an increased cardiovascular risk from tolbutamide. The studies were criticized by proponents of the UGDP trial because of the relatively small number of patients involved and because the baseline characteristics of the treatment groups were not fully reported. 95/

A third study which received little attention in oral testimony was provided for the hearings record by Pfizer Inc. in response to a letter from staff economist Benjamin Gordon offering the pharmaceutical company an opportunity to present its views on the oral hypoglycemics controversy. 96/ This report on diabetes and congestive heart failure came out of the now famous long-term epidemiological study known simply as the Framingham Study. The investigators determined the incidence of congestive heart failure in relation to prior diabetic status in 5,209 men and women over an 18 year period. One of the study's findings was

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94/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13348.

95/ Ibid., pp. 10793, 10794, 10904, 10994, 13259.

96/ Kannel, William B., Marthana Hjortland, and William P. Castelli. Role of Diabetes in Congestive Heart Failure: The Framingham Study. The American Journal of Cardiology, July, 1974: 29-34.

the "lack of any discernible increased risk of congestive heart failure in the group treated with tolbutamide or diet." 97/

B. 1975-1978

Most current research on oral hypoglycemic agents has focused on their pharmacologic action. Scientists are trying to find out how these drugs lower blood sugar and what other effects they might have in various organs and tissues. There have been no long-term prospective trials, published since the hearings, which compare diabetes treatments.

One recent report from the Coronary Drug Project (CDP) looked at the relationship between plasma glucose levels and risk of death in 2770 male survivors of myocardial infarction over a five-year follow-up period. 98/ The investigators found some evidence of an increased mortality risk in users of oral hypoglycemic agents over that of nonusers in men with elevated glucose levels. These researchers emphasized, however, that "the results must be interpreted with great caution both because they are of only borderline statistical significance and also because various factors not recorded in the CDP might have influenced the results." 99/

In a letter to The Lancet, Dr. B.S. Raheja reported the results of a retrospective study which supported the UGDP findings. 100/ His

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97/ Kannel, William B. et al., (1974) op. cit., p. 34. [see footnote 96/]

98/ Coronary Drug Project Research Group, Baltimore. The Prognostic Importance of Plasma Glucose Levels and the Use of Oral Hypoglycemic Drugs After Myocardial Infarction in Men. Diabetes, May, 1977: 453-465.

99/ Ibid., p. 453.

100/ Raheja, B.S. Letter: Hypoglycemic Agents in Diabetes Mellitus. The Lancet, Feb. 28, 1976: 495.

subjects included 120 maturity-onset diabetics who had suffered acute myocardial infarctions. Dr. Raheja observed that patients treated with diet alone had fewer fatal and non-fatal cardiac episodes compared to patients treated with either sulfonylureas or insulin. The cardiac episodes also occurred earlier in patients taking sulfonylureas. Dr. Raheja added that the patients in the three treatment groups (insulin, sulfonylureas, and diet) were comparable in age, sex, serum cholesterol levels, blood pressure, and smoking habits. It must be remembered, however, that Dr. Raheja's conclusion is based on a very small number of cases and that his study has all the usual problems of interpretation to which retrospective studies are subject.

Another retrospective study of rather greater size was reported more recently. 101/ This study compared mortality from coronary heart disease in 5,210 diabetic patients to that in the general population of Warsaw, Poland. The investigators reported,

> The standardized mortality ratios from CHD [coronary heart disease] in men were not related to the hypoglycemic therapy administered at the onset or during the course of diabetes. In women the highest mortality was in the group treated with insulin, intermediate in the group treated with oral agents and lowest in the group treated only with diet. These findings do not seem to confirm the assumption that oral hypoglycemic agents increase the risk of cardiovascular deaths. 102/

101/ Krolewski, Andrzej S., Artur Czyzyk, Danuta Janeczko, and Jan Kopczynski. The Fates of Diabetic Patients -- Warsaw Epidemiological Study II: Mortality from Coronary Heart Disease Among Patients in Relation to Methods of Hypoglycemic Treatment. Acta Medica Polona, March, 1977: 213-230.

102/ Ibid., p. 213.

IV. LACTIC ACIDOSIS AND ORAL HYPOGLYCEMIC AGENTS

Lactic acidosis is a metabolic disorder in which abnormal amounts of lactic acid accumulate in the blood. Early symptoms may include weakness, lethargy, malaise, increased respiration, abdominal pain, nausea, and vomiting. As the condition progresses, stupor and coma occur. Cardiovascular collapse and death frequently result. A risk of developing lactic acidosis has been associated with the use of phenformin, a biguanide compound, but not with the use of sulfonylureas, the class of drugs to which tolbutamide belongs.

A. 1974-1975 Hearings

While lactic acidosis is a serious condition which proves to be fatal in about 50 percent of the cases, it was not a major or controversial topic, as was cardiovascular toxicity, and so received little attention during the hearings.

In his 1974 written testimony, Dr. Robert F. Bradley listed lactic acidosis as one of the side-effects associated with phenformin use. According to Dr. Bradley, there is

> a tendency for lactic acidosis to appear more readily in individuals who are taking phenformin. When lactic acidosis occurs it is often fatal, usually because of the extremely serious nature of the underlying condition. Lactic acidosis readily occurs in individuals with or without diabetes who become acutely ill from a variety of causes and regardless of any medication they may be taking, but it has been observed in somewhat greater frequency in the diabetic taking phenformin. 103/

103/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10981-10982.

Dr. Bradley noted that side-effects and even toxicity can be anticiapted from the use of any drug. He does not believe that the adverse reactions, among which is lactic acidosis, to oral hypoglycemic drugs occur "with sufficient regularity to warrant discontinuance of the use of these drugs," although they do warrant proper use of those compounds." 104/

During the 1975 sessions, Dr. J. Richard Crout, Director of the FDA Bureau of Drugs, testified,

> Let me state the reason why the benefit to risk [ratio] for phenformin is less than for the other drugs. This drug may cause lactic acidosis, a potentially fatal complication in patients who take it. So, there is a clear added hazard, in addition to what it does to cardiovascular mortality.
>
> Now, the incidence of that lactic acidosis has in the past been thought to be quite low. As more and more information comes along, it looks like it is higher than we had anticipated. And that issue of lactic acidosis was brought before our Metabolic and Endocrine Advisory Committee more than a year ago.
>
> At that time they recommended that a warning be placed on the drug, but that it stay on the market. We are going to take the issue back to that committee and take up that issue again. 105/

When questioned by staff economist Benjamin Gordon on the medical justification for keeping phenformin on the market, Dr. Crout replied that he could see no such justification.

> MR. GORDON. As a medical scientist, could you tell us what that medical justification is for having this drug on the market?
>
> DR. CROUT. What my personal opinion is?
>
> MR. GORDON. Yes.
>
> DR. CROUT. I would support Dr. Winegrad. I

104/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10981.

105/ Ibid., p. 13297.

personally would not use the drug.
MR. GORDON. Then you see no reason for this drug to be on the market. Is that correct?
DR. CROUT. You are asking me as a medical scientist?
MR. GORDON. As a medical scientist.
DR. CROUT. As a medical scientist, yes, I don't see any such reason. 106/

Dr. Crout's opinion was shared by several other witnesses. 107/

B. 1975-1978

Although discussed at length in connection with cardiovascular and total mortality, the UGDP study was not referred to during the hearings in the brief discussions of lactic acidosis. In their 1975 publication, the UGDP investigators did, however, report three cases of lactic acidosis, one of which was fatal, among the 204 phenformin users. No cases of lactic acidosis were reported for the 823 patients treated with other forms of therapy. 108/

Data reported in 1976 from a hospital in South Australia revealed 15 cases of phenformin-associated lactic acidosis over a two-year period. 109/ These data were later used to estimate that for every 1,000 phenformin users, 12 would develop lactic acidosis. 110/

106/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13297.

107/ Ibid., pp. 10843, 1o844, 11023, 13297, 13325, 13326.

108/ The University Group Diabetes Program, (1975) op. cit. [see footnote 86/]

109/ Wise, P.H., et al. Phenformin and Lactic Acidosis. British Medical Journal, Jan. 10, 1976: 70-72.

110/ Phillips, P.J., D.W. Thomas, and P.E. Harding. Letter: Biguanides and Lactic Acidosis. British Medical Journal, Jan. 22, 1977: 234.

Dr. Ulf Bergman of the Karolinska Institute presented data on the number of recent cases of phenformin-associated lactic acidosis in Sweden at the April, 1977 meeting of the World Health Organization. For the years 1974 to 1976, Bergman reported, there were 27 such cases. 111/

These and several other reports of lactic acidosis associated with phenformin use were made to the FDA Bureau of Drugs Endocrinology and Metabolism Advisory Committee. 112/ After evaluating the published reports and hearing presentations from FDA personnel and the Ciba-Geigy Corporation, a phenformin manufacturer, the advisory committee concluded that "an unequivocal association existed between the use of phenformin and the occurrence of lactic acidosis." The committee added that the relationship was probably causal "although the mechanism of causality was not clear." 113/ The committee unanimously recommended that phenformin be taken off the market.

HEW Secretary Joseph A. Califano, Jr. took the committee's advice. On July 25, 1977 he issued a report suspending the New Drug Applications for phenformin. In issuing this report the Secretary took an unprecedented step, invoking the "imminent hazard" provision of the Federal Food, Drug, and Cosmetic Act. This provision gives special authority only to the

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111/ U.S. Department of Health, Education, and Welfare. Office of the Secretary. Order of the Secretary Suspending Approval, New Drug Applications for Phenformin. July 25, 1977, p. 66. [Hereinafter referred to as The Secretary's Order, July 25, 1977. See Appendix G for the summary section from that order.]

112/ Committee members are listed in Appendix H.

113/ The Secretary's Order, July 25, 1977, p. 3 [See Appendix G].

Secretary of Health, Education, and Welfare, enabling him to immediately remove from the market any drug that represents an imminent hazard to the public health. Secretary Califano believed that phenformin presented such a hazard.

The Secretary's order provided a 90-day transition period during which time physicians could re-evaluate their patients taking phenformin and switch them to alternate therapies. 114/ The order also noted,

> A small patient population does exist, however, that may be particularly benefited by the continued availability of phenformin to them. 115/

The Secretary therefore ordered that discussions be initiated

> with the manufacturers and professional associations to devise a voluntary controlled distribution system which will assure the continued availability of the drug to only the limited population for whom the benefits outweigh the risk. If such a distribution system can be established, the suspension could be modified. Alternatively, phenformin could be made available on a restricted basis to appropriate patients under the investigational new (IND) authority of the Federal Food, Drug, and Cosmetic Act. 116/

No distribution arrangement was found, however, which was acceptable to the FDA, the manufacturers, and the American Medical Association. 117/ Phenformin was, therefore, removed from the market October 23, 1977, and all outstanding stocks were recalled.

114/ The Secretary's Order, July 25, 1977, p. 12. [See Appendix G]

115/ Ibid., p. 13.

116/ Ibid., p. 14.

117/ HEW NEWS Release, P77-41, Oct. 22, 1977, p. 2.

V. HYPOGLYCEMIA AND ORAL HYPOGLYCEMIC AGENTS

Hypoglycemia is defined as "an abnormally diminished content of glucose in the blood." 118/ The condition can be serious, leading to tremulousness, cold sweat, piloerection, hypothermia, and headache accompanied by confusion, hallucination, bizarre behavior, and, ultimately, convulsions and coma.

The hypoglycemic agents, as their name implies, lower blood sugar. The sulfonylureas, the group of compounds to which tolbutamide belongs, seem to lower blood sugar by stimulating insulin production and secretion. The biguanides, including phenformin, differ significantly from the sulfonylureas in the mechanism of their hypoglycemic effect. Scientists think that phenformin works in three ways: (1) it increases glucose utilization; (2) it decreases the formation of glucose by the liver; and (3) it inhibits the intestinal absorption of glucose. 119/

There are no strict doses rigidly prescribed for oral hypoglycemic agents. The dose is varied to meet the changing needs of the individual patient. It is always possible that a given dose of oral agent might turn out to be too large for a particular patient. Or the patient, having "sinned" on his diet, may take more of the drug than he is supposed to. When this happens the blood sugar can be lowered too much and a hypoglycemic reaction can occur. Such reactions are usually limited to diabetics taking

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118/ Dorland's Illustrated Medical Dictionary. 25th Edition. W.B. Saunders Company, 1974: 750.

119/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 13415, 13419.

sulfonylureas. Phenformin, since it does not affect insulin secretion, does not readily induce hypoglycemia. 120/

A. 1974-1975 Hearings

The possibility of abnormally low blood sugar resulting from hypoglycemic agents was discussed with particular emphasis on the second generation oral agents. These relatively new compounds (including glyburide, glyhexamide, glycodiazine, and glybenclamide) exhibit far greater hypoglycemic activity than the currently available oral agents. In his testimony, Dr. Thaddeus E. Prout of Johns Hopkins University estimated that the "hypoglycemic potency of these new agents is somewhere between 100 and perhaps 200 times greater than that of the presently available agents." 121/ Dr. Christian R. Klimt testified that these drugs "are so potent that a slight overmedication either by a physician or by patient error leads to irreversible hypoglycemic shock and death, a fact which has been brought out by a meeting in Dusseldorf in 1971 where by general account, some 200 deaths had already occurred from an overdose of these drugs." 122/

At the time of the hearings, New Drug Applications for the second generation oral hypoglycemic agents had been submitted to the Food and Drug Administration for approval. It was generally felt that such

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120/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13419.

121/ Ibid., p. 10777.

122/ Ibid., p. 10768.

approval should not be given until the drugs were adequately tested to prove: (1) their safety and (2) their superiority over currently available agents in controlling blood sugar. 123/ Dr. Klimt felt that "the drug industry should be asked to finance such studies even if provisional licenses are granted." 124/

In his written testimony for the 1974 sessions, FDA Commissioner Schmidt stated that hypoglycemia can occur with any of the sulfonylureas. The new sulfonylureas, such as glyburide, are more potent; they require "careful titration of dosage by the doctor, particularly in elderly patients, and careful instructions to the patient never to exceed the designated dose lest severe hypoglycemic reactions occur." 125/ With respect to the New Drug Applications for the second generation oral agents, Dr. Schmidt wrote:

> In the new drug application for glyburide, controlled studies comparing tolazamide or tolbutamide with glyburide revealed no significant differences in incidence of hypoglycemic reactions. There were no hypoglycemic deaths reported in the clinical studies to date among over 3,000 U.S. patients treated with glyburide, although our current information is that 25 deaths have occurred in Germany. However, no deaths have been reported to us from Great Britain or Canada, and the drug has been marketed in those countries since 1970.
>
> Our review of the data in the new drug

123/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10777, 10807, 11088, 11112.

124/ Ibid., p. 11088.

125/ Ibid., p. 10915.

> application led us to a conclusion in 1973 that safety and efficacy had been demonstrated, but approval for marketing was withheld until labeling for the oral agents could be finalized. Since then, however, in view of the evidence of excess deaths in Germany, additional study of this problem is essential. We have asked the manufacturers to obtain more information on the circumstances of these deaths. Therefore, no final decisions can be made at this time. 126/

In his written statement, Dr. Thaddeus E. Prout discussed the hypoglycemic hazard associated with the oral agents in no uncertain terms:

> Not enough has been made, however, of the fact that these are potent hypoglycemic agents for which the case fatality rate is somewhere between 15 and 20 percent. In plain language, this states that an agent which has been used as a drug of convenience has been shown to have an uncontrollable ability to lower blood sugar to symptomatic levels. Among the reported cases, between one-fifth and one-sixth of such patients have died when hypoglycemia occurred in association with oral hypoglycemic agents, with or without concomitant use of other drugs. This evidence has accumulated over more than a decade in the use of agents which are relatively impotent by current knowledge and in the hands of practitioners who have had optimal experience in their regulation. 127/

126/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10915-10916.

127/ Ibid., pp. 11110-11111.

Based on the medical community's experience with the currently available oral hypoglycemic agents, Dr. Prout felt "There can literally be no justification for the introduction of a second generation of these medications which are even more potent hypoglycemic agents." 128/

B. 1975-1978

The current scientific literature contains no long-term trials such as those recommended during the hearings to evaluate the second generation hypoglycemic agents and their potential for causing irreversible hypoglycemia. There has been one report, however, of hypoglycemia apparently related to the currently available oral agents. 129/

Dr. Roger W. Turkington reported three cases of severe hypoglycemic encephalopathy (brain disease) in maturity-onset diabetics. The first patient was being treated with chlorpropamide, a sulfonylurea, when symptoms appeared. The second patient was receiving tolbutamide and phenformin and the third was taking chlorpropamide and phenformin when the signs of encephalopathy began. Each of these patients experienced disabling neurological deficits following the onset of oral hypoglycemic therapy. The ensuing encephalopathy was characteristic of hypoglycemia, wrote Dr. Turkington, "in that it involved primarily the 'highest' intellectual functions (mathematical calculations, musical performance, judgement, etc.) at the onset, then progressed to involve speech and

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128/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 11111.

129/ Turkington, Roger W. Encephalopathy Induced by Oral Hypoglycemic Drugs. AMA Archives of Internal Medicine, August, 1977: 1082-1083.

motor functions." 130/ In two of the cases the encephalopathy progressed to irreversible diffuse cortical atrophy. Dr. Turkington added that the recommended maximal doses of the drugs were not exceeded and that there was no evidence for any instance of overdosage or self-medication. He concluded,

> Several similar cases have been observed in a large diabetes referral practice, and it is possible that hypoglycemic drug-induced encephalopathy may occur less rarely than the paucity of literature reports would indicate. In view of the controversial nature of these drugs, the cases reported here indicate the need for further caution in the administration of oral hypoglycemic agents to avoid such disastrous adverse effects. 131/

130/ Turkington, Roger W., (1977) op. cit., p. 1083. [see footnote 129/]

131/ Ibid., p. 1083.

VI. WEIGHT CONTROL AND ORAL HYPOGLYCEMIC AGENTS

It has been estimated that "90 percent of all diabetics are over the age of 40 when they are first found and that the majority of this older group are obese by any standards." 132/ Obesity is now recognized as a major factor which predisposes a genetically susceptible individual to diabetes. Obesity and excessive caloric intake stress the beta cells of the pancreas making them produce more insulin. Despite the higher than normal insulin levels, however, plasma glucose continues to rise. Weight reduction and control, then, are always essential steps in treating the obese, maturity-onset diabetic. 133/

A. 1974-1975 Hearings

Despite the central role obesity plays in the etiology of maturity-onset diabetes, the relationship between weight control and oral hypoglycemic drugs received little attention during the hearings. One reason might have been the almost exclusive concern with the UGDP study which did not specifically address the problem of weight control. In his testimony, Dr. John K. Davidson of Grady Memorial Hospital commented, "Unfortunately, the [UGDP] study did not evaluate obesity as a risk factor related to the development of morbidity or premature mortality in maturity-onset diabetes mellitus." 134/

132/ The 1974-1975 Oral Hypoglycemics Drugs Hearings, p. 10761.

133/ Ibid., p. 10897

134/ Ibid., p. 10839.

During the 1975 sessions, obesity was considered at some length by Dr. Ethan A.H. Sims of the University of Vermont College of Medicine. Dr. Sims explained, "Insulin, in addition to its well known function of lowering blood glucose, is a hormone which promotes the deposition of fat." 135/ The sulfonylureas, by stimulating the release of insulin, "promote fatness," according to Dr. Sims. 136/ Dr. Sims also explained that in the obesity-induced, adult-onset diabetic, who is initially not dependent upon insulin therapy,

> there is a resistance to the action of insulin of both muscle and the fat. The insulin in the blood is actually increased, but it is inadequate in the face of the resistance for the normal metabolism of food. This produces a stress on the pancreatic islets, which may ultimately be followed by failure and development of insulin-dependent diabetes. 137/

Dr. Sims and his colleagues have been able to produce this sort of insulin resistance in research volunteers through deliberate weight gain even though none of the volunteers had family histories of either diabetes or obesity. Such insulin resistance, developing secondarily to obesity and overeating, is completely reversible.

Dr. Sims testified that the patients in the tolbutamide and insulin groups in the UGDP study actually gained weight.

> In all of the five groups there was a loss of about 3 percent of the body weight initially, as a result of the moderate dietary restriction which they were all given. The placebo group and the phenformin group maintained this loss throughout this study. But, in this, the

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135/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13329.

136/ Ibid., p. 13677.

137/ Ibid., p. 13330.

> phenformin group was actually no better than the placebo. On the other hand, patients in both the tolbutamide and the two insulin groups, not only regained the weight initially lost, but gained well above their original baseline. So, there is a considerable difference in the study between the weight of those receiving insulin or sulfonylureas as opposed to the placebo group. 138/

Dr. Sims believes that the preoccupation with cardiovascular mortality in the UGDP study has blurred the importance of weight control and that any label for sulfonylureas should reflect the central role of diet and exercise in controlling diabetes. "Untreated obesity," he wrote, "may pose a greater long-term risk in relation to cardiovascular and other disease than the use of oral agents." 139/

In discussing his experience in treating diabetics at Grady Memorial Hospital, which has the largest known diabetic population of any teaching hospital in the United States, Dr. Davidson testified that "the patients tended to gain weight on both glyburide and tolbutamide therapy." 140/ Both of these drugs are sulfonylureas and work by stimulating the release of insulin. Dr. Davidson listed eight principles which underlie the strategy used in treating diabetes at Grady. Included in these were the statements:

> Obesity is an absolute contraindication to the use of sulfonylurea agents.

138/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13331.

139/ Ibid., p. 13676.

140/ Ibid., p. 10841.

> Insulin therapy should be used in the obese diabetic only if the diabetes acutely decompensates (plasma glucose 500 mg/dl or above or moderate to large acetonuria) or if clinically significant neuropathy is present. 141/

In other words, sulfonylureas should never be used to treat obese diabetics; insulin should be used in the obese only if dietary therapy does not work well enough or if some neurologic condition, which necessitates careful blood sugar control, is present.

Oral hypoglycemic agents have an indirect, as well as a direct, effect on weight control. Dr. Davidson testified that by their very convenience, the oral agents tend to make both physicians and patients neglect dietary therapy and weight reduction. 142/

B. 1975-1978

There have been no reports in the recent scientific literature linking sulfonylureas with weight gain in maturity-onset diabetes. In theory, the accepted form of therapy for this disease is still centered around weight reduction and careful dietary control, sulfonylureas being used only when dietary measures prove inadequate. 143/

141/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 11023.

142/ Ibid., p. 10852.

143/ Bierman, E.L. The Oral Antidiabetic Agents. American Family Physician, Jan., 1976: 98-104.

VII. HEALTH BENEFITS OF ORAL HYPOGLYCEMIC AGENTS

Do oral hypoglycemic agents prevent or delay the long-term consequences of diabetes mellitus and prolong the lives of maturity-onset diabetics? This question, important in any discussion of oral hypoglycemic drugs, has been largely obscured by the controversy over the drugs' possible toxicity. 144/

Diabetes mellitus is a disorder of carbohydrate metabolism, one of the consequences of which is elevated blood sugar and, usually, the appearance of sugar in the urine. Scientists cannot cure the underlying metabolic disorder, but they can control blood sugar and thus relieve some of the more uncomfortable symptoms of the disease. For years the standard therapy for diabetes mellitus, whether it was symptomatic or not, has involved the strict control of blood sugar. For years physicians have hoped that by controlling blood sugar they were somehow delaying the serious consequences of diabetes and prolonging their patients' lives. Many physicians who use insulin or oral agents reason that, since elevated blood sugar is associated with an increase in atherosclerotic complications, normalization of blood sugar may decrease the incidence of these complications. This reasoning has yet, however, to be proven by evidence from controlled clinical trials.

144/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10917.

A. 1974-1975 Hearings

There are perfectly valid and essential reasons for controlling blood sugar in diabetes mellitus. Dr. Edward M. Chester of Case Western Reserve University detailed some of these reasons in his 1975 testimony.

> Well, we do accomplish a variety of things. If the blood sugar level becomes excessive, then the amount of urine, salt, et cetera, are passed out into the urine, and the patient not only loses tremendous amounts of water and becomes dehydrated, but may suffer from some of the loss of the electrolytes.
>
> Second, continuation of poorly controlled diabetes, again measured by levels of blood sugar, may be followed by a variety of very serious manifestations. One is diabetic ketoacidsosis, where presumably, because of lack of insulin and other factors, large amounts of the fat are broken down, mobilized, converted to a number of substances known as ketone bodies. As these substances accumulate, the patient may become unconscious and death may follow.
>
> There is a comparable state in which the blood sugar reaches extremely high levels, perhaps in the range of 1,000 or above, where extreme loss of water becomes critical. These patients may become unconscious and die within a relatively short period of time if not treated adequately.
>
> There is also the question of whether or not keeping blood sugar at given levels will prevent infection. This is difficult to document. What we do know, however, is that the individual with diabetes who develops infection, unless we treat the diabetes vigorously and simultaneously treat the infection, the patient is likely to suffer and may die.
>
> So, there are reasons to try to reach given levels of blood sugar. 145/

145/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13313.

Witnesses at the hearings generally agreed, however, that the value of controlling blood sugar in preventing the vascular and neurologic complications of diabetes is a matter for conjecture. 146/

The UGDP study was, in fact, designed to answer questions about the long-term value of oral hypoglycemic therapy. 147/ Preliminary results from this study have indicated that the strict control of blood sugar probably does not help the patient in the long run. 148/ The UGDP findings can never be considered conclusive, however, because tolbutamide and phenformin therapies were discontinued before the results reached statistical significance. Even so, Dr. Frank Davidoff testified that the UGDP data "are the most convincing ever assembled demonstrating ineffectiveness of not only the oral agents, as they were employed in the study, but also of insulin, in preventing the long-term vascular and neuropathic complications of the disease." 149/

Aside from eliminating the overt symptoms of the disease, there seemed little justification, based on the scientific evidence available at the time of the hearings, to strictly control blood sugar. Dr. Davidoff described, in his written testimony, what he believed to be the reasons

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146/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10762, 10810, 10811, 10858, 10898, 10917, 10980, 11009, 11010, 11011, 11012, 11126, 13264, 13302, 13311, 13313, 13318, 13325, 13656, 13660, 13661, 13672, 13687, 13709.

147/ Ibid., pp. 10762, 10899.

148/ Ibid., p. 10811.

149/ Ibid., p. 11009.

for the current methods of treatment for and manner of thinking about diabetes.

> The first reason is historical: Sugar has been the hallmark, almost the definition of the disease for several hundred years, ever since Dr. Robert Wyatt tasted the urine of one of his patients in 1774 and found it sweet. When science entered medicine in the 19th century, the chemistry of sugars had already far outstripped that of proteins and fats. The facts are that diabetes is fundamentally a disease of proteins, not of sugars; it kills acutely by deranging fat metabolism, or it kills slowly by mechanisms which are still entirely obscure, but these facts have been less easy to keep in mind than the more obvious day-to-day derangements in sugar metabolism.
>
> The second is a matter of technology and convenience. Sugar measurements are still among the quickest, cheapest, and most accurate in medicine. This makes sugar levels the most convenient way to measure day-to-day disease activity; but the fact remains that blood sugar levels may have no direct relationship to the real abnormality ultimately responsible for the chronic disability and death of the patient. This focus on sugar has also had more than trivial complications for pharmacology, since, with few exceptions, the screening process for new chemical and biological agents to treat diabetes depends entirely upon their ability to lower blood sugar. Perhaps the lesson here should be that in our haste to achieve control and cure of diseases we should not rely on a superficial analysis of the nature of the disease, but work to obtain enough fundamental biological information to be reasonably confident we are measuring the right thing. The implied need for basic research is obvious.
>
> Thirdly, when we go to effort and expense to show that something is abnormal, even though it be only a number like blood sugar, there is an almost irresistable urge to make it normal again. And if we as physicians decline to treat in this situation, the patient may well communicate the expectation that we should be treating.
>
> Fourthly, there is an important psychological need among physicians to believe that a connection exists between process and outcome, that is, control of blood sugar and control of disease.

> This need was most poignantly expressed to me several years ago by a diabetologist physician, himself a diabetic, who put it thus: 'You can't effectively precribe a treatment in which you are only half a believer.'
>
> Fifthly, even though many physicians may be unconvinved by the evidence that control of blood sugar really affects long-term outcome, most would also agree the evidence is not yet all in; there remains a reasonable doubt. As a result, many take the position that one should give the patient the benefit of the doubt. Suppose, they say, in 25 years it turns out that vigorous 'treatment of the blood sugar' does protect the patient's vascular system; we would feel badly if we hadn't treated.
>
> Finally, in addition to historical, intellectual, and psychological reasons for treating to control the blood sugar, there are important social determinants in the prescription process. Dr. Muller has described these pressures succinctly as follows: "Prescribing is, theoretically at least, a means of terminating the interview in a fashion that satisfies both doctor and patient....the prescription is a signal for the approaching end of the encounter, it both summarizes and carries forward the relationship, it is an expression of concern, and it deals with the interests of both parties in a manner perceived as equitable". 150/

Some indirect evidence for the ineffectiveness of oral hypoglycemic drugs in prolonging the lives of maturity-onset diabetics was discussed by Drs. Chalmers, Miller and Davidson. 151/ These witnesses presented statistics and graphs indicating that the life expectancy for maturity-onset diabetics has been decreasing since the early 1960's when the oral agents came into widespread use. The World Health Organization

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150/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 11011-11012.

151/ Ibid., pp. 10794, 10795, 10852, 10996.

discussed this apparent rise in mortality in a 1971 news release printed in the hearings record. 152/ The article raised the question, "Has mortality been increased by the use of oral hypoglycemic agents, which came into vogue not many years ago and are now extensively prescribed?" 153/

Dr. Miller testified that the Japanese have also noted a rise in the mortality rate among older diabetics coincident with the introduction of the oral agents. 154/ Some witnesses suggested that the oral hypoglycemic agents might be responsible for the increased death rate, a phenomenon not observed among juvenile diabetics for whom the oral agents are never prescribed. 155/ While the oral agents might not be causing the decreased life expectancy in maturity-onset diabetics, it seems at least possible that they are not prolonging life.

One further shortcoming of the oral agents discussed in relation to their disputed long-term benefits is their loss of effectiveness with continued use. It appears that after several years of therapy, a patient loses responsiveness to the oral hypoglycemic drugs; the drugs lose their ability to lower the patient's blood sugar. This condition is termed secondary failure. According to Edward M. Chester, a number of studies

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152/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 11232-11234.

153/ Ibid., p. 11232.

154/ Ibid., p. 10795.

155/ Ibid., p. 10794.

have reported on tolbutamide's ineffectiveness after several years of continuous therapy. In one of these studies, only about 13 percent of the patients were still responding to tolbutamide after five years of therapy. 156/

Evidence refuting the notion that oral hypoglycemic agents are ineffective in prolonging the lives of adult-onset diabetics was provided for the hearing record by pharmaceutical companies and private physicians. 157/ In an article submitted by Pfizer Inc., Drs. James M. Moss and DeWitt E. DeLawter of the Georgetown University School of Medicine concluded that "sulfonylurea drugs have a beneficial effect upon longevity when they are used properly." 158/ This conclusion was based on an analysis of the records of 1,840 maturity-onset diabetics. The authors stated, "According to the predictions of life-insurance tables, these patients lived longer than non-diabetic patients. There was a significant decrease in longevity in those who had persistent hyperglycemia. The greatest increase in longevity occurred in those whose disease could be controlled by diet alone or with sulfonylurea drugs." 159/

Although he did not testify in person, Dr. Moss did submit a written statement to the Subcommittee. In that statement he wrote,

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156/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13647.

157/ Ibid., pp. 11548-11613.

158/ Moss, James M. and DeWitt E. DeLawter, Long-Term Results with Oral Hypoglycemic Drugs. Journal of the American Geriatrics Society, v. 21, 1973: 72-76.

159/ Ibid., p. 72.

> Because there is no ethical way that long term placebo controls can be used in a treatable disease, we have been forced to compare our results to the life insurance tables of non-diabetics of the same age. We found that our patients treated with sulfonylurea drugs live about 9% longer than predicted by these tables. There is no evidence that we shortened the life of any of our patients by using these drugs, even though we have used them in three times as many patients for twice as many years as did the UGDP group. There is evidence that the patients treated with these drugs had less morbidity, fewer symptoms, and lived longer than did those who were not treated. 160/

While Alexander Marble of Harvard Medical School agreed that vascular disease could be controlled by controlling blood sugar in insulin-requiring diabetics, he did not believe the case to be so clear-cut with adult-onset diabetics who do not need to take insulin. In one of his review articles provided for the hearing record, Dr. Marble stated, "In my opinion, there is abundant evidence to indicate that, in a person with onset of insulin-requiring diabetes under the age of 30 years, vascular disease can be lessened and postponed by consistently good 'chemical' control of diabetes. However, no one has the final and complete answer, particularly concerning middle-aged and elderly persons with stable, noninsulin-requiring diabetes in whom oral hypoglycemic agents are useful." 161/

160/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 11135-11136.

161/ Ibid., p. 11612.

B. 1975-1978

The notion that oral hypoglycemic agents may prevent the long-term complications of diabetes and prolong life has not been supported by the recent literature. Neither Shen and Bressler 162/ nor Tan et al. 163/ were able to demonstrate a sustained lowering of blood glucose levels by either tolbutamide or phenformin. Tan et al. did find more patients with normal blood glucose levels after one year of chlorpropamide treatment than any other form of therapy. 164/ Dr. Tan and colleagues believe that the necessity of long term therapy with oral hypoglycemic agents in diabetes needs to be redetermined.

Drs. Shen and Bressler were more unequivocal in their conclusions. These investigators wrote:

> The failure of tolbutamide or phenformin to achieve a sustained lowering of blood glucose levels in the treated populations obviates any need to be concerned with their reputed toxicity. There is no reason to use a drug that does not work. Since neither agent caused a sustained lowering of the blood sugar of the populations studied no question of gain versus risk can be raised. Even the safest drug is of no value if it has no efficacy. 165/

162/ Shen, Shiao-Wei and Rubin Bressler. Clinical Pharmacology of Oral Antidiabetic Agents. The New England Journal of Medicine, April 7, 1977: 787-793.

163/ Tan, M.H. et al. The Effects of Long-Term Therapy with Oral Hypoglycemic Agents on the Oral Glucose Tolerance Test Dynamics in Male Chemical Diabetics. Diabetes, June, 1977: 561-570.

164/ Ibid., p. 567.

165/ Shen and Bressler, (1977) op. cit., p. 792.

In the most recent publication from the UGDP, 166/ it was concluded that the data "provide no evidence that insulin or any other drug lowering blood glucose levels will alter the course of vascular complications in the type of diabetes that it most common, adult-onset diabetes." 167/

166/ University Group Diabetes Program. Effects of Hypoglycemic Agents on Vascular Complications in Patients with Adult-Onset Diabetes. VII. Mortality and Selected Nonfatal Events with Insulin Treatment. Journal of the American Medical Association, July 7, 1978: 37-42.

167/ Ibid., p. 42.

VIII. THE FDA, POLICY ISSUES, AND ORAL HYPOGLYCEMIC AGENTS

A. Role of the Food and Drug Administration

The Food and Drug Administration is responsible both for evaluating the safety and efficacy of drugs used in this country and ensuring that these drugs are properly labeled and advertised. It is this responsibility which has put the FDA squarely in the center of the oral hypoglycemics controversy and has brought the agency criticisms from UGDP proponents and opponents alike.

The Committee for the Care of the Diabetic has charged that the FDA is biased in favor of the UGDP study 168/ and has insisted that both sides of the scientific controversy be presented on the required labeling for oral hypoglycemic drugs. 169/ Neil L. Chayet, the committee's legal counsel, went so far as to charge the Government with a "cover-up" and testified that the FDA has been trying to squelch the controversy, reporting only those research findings that support the UGDP study. 170/ According to Mr. Chayet, "the Committee for the Care of the Diabetic will go back to court, and will take every step it has to take, to prevent a one-sided, biased label from emerging; and the Biometric Society Study does not alter our resolve." 171/

168/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13623.

169/ Ibid., pp. 13278, 13281, 13282, 13284, 13622.

170/ Ibid., pp. 13282, 13625, 13626.

171/ Ibid., p. 13281.

Scientists who support the findings of the UGDP study have criticized the FDA for dragging its feet in failing to implement new labeling for oral hypoglycemic drugs. Dr. John K. Davidson of Grady Memorial Hospital summed up this criticism when he testified,

> In my opinion, the Food and Drug Administration has been negligent in the extreme in not providing properly written package inserts for the sulfonylureas and phenformin, so that physicians can know honestly and fully the inherent dangers in their use, and so that the drug-consuming public can become aware of and be protected from these dangers. I trust that the Congress, and this committee in particular, will prevail on the FDA to mend its errant ways in these matters in the near future. It is time to bring a halt to the delays occasioned by the Bureau of Drugs over the last 4 years. It is clear to me that the Bureau has abandoned responsible scientific evaluation and has been trying to match the contents of the package inserts to current medical practice rather than to scientific merit. 172/

Throughout the controversy the Food and Drug Administration has insisted that it supports that findings of the UGDP study and the necessity for new labeling to reflect these findings. FDA Commissioner Schmidt testified,

> Now, as you know, Mr. Chairman, it has been the view of the FDA since 1970, that the findings of the UGDP study should be reflected in a warning in the labeling for oral hypoglycemic drugs and in turn, in the use by physicians of these drugs. 173/

It is the agency's responsibility, according to Dr. Schmidt, to issue a warning when enough evidence exists to support one. Dr. Schmidt does not believe, however, that the FDA has a responsibility for controlling the

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172/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10844.

173/ Ibid., p. 13299.

prescribing behavior of the American physician. "Part of this problem," he testified, "belongs squarely with the medical profession, with the educational institutions, of (sic) the lack of continuing education programs." 174/

Dr. Schmidt reminded the Subcommittee that the agency's attempts to require a warning label for oral hypoglycemic drugs was stopped by the courts. The rather cautious approach the FDA has followed since that time has been part of an attempt to avoid further litigation. 175/

Peter Barton Hutt, then the Assistant General Counsel of HEW's Food and Drug Division, explained to the Subcommittee,

> 'Any citizen has the right to take us to court. We would concede standing in the courts to any citizen to challenge action of any kind, whether to require a warning or not to require a warning...That is why I am saying that we must be careful that this time we have an absolutely irrefutable scientific base on which to rely so that we will win that challenge if and when it occurs. 176/

The irrefutable base to which Mr. Hutt referred was supposed to be the review of the UGDP study by the Biometrics Society. That review did not have the desired effect, however, and the controversy continued.

Dr. Angela J. Bowen, whose testimony at FDA's 1975 hearing on proposed labeling for oral hypoglycemic drugs was instrumental in bringing about an audit of the UGDP's raw data, discussed the agency's

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174/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10873.

175/ Ibid., p. 13291.

176/ Ibid., p. 10874.

role in drug regulation in a 1976 article. 177/ In that article she wrote,

> 'There are concerns here that greatly overshadow the oral hypoglycemics and whether or how they should be used. The Food and Drug Administration has apparently chosen this study and oral hypoglycemics to implement three major changes in policy.
>
> First, the Commissioner wants to begin to designate the 'Drug of Choice' for the treatment of most major disease categories;
>
> Second, the FDA is seeking to institute 'class labeling.' That is to say, if one drug of a class of similar compounds is found to have any given side effect the labels of the entire class will be changed to reflect that side effect;
>
> Third, the Commissioner wants to act as the independent arbiter in situations where there is medical controversy. 178/

Dr. Bowen fears that these policy changes seriously threaten "the right of the physician to select what is considered to be the proper therapy for the individual, to make a decision based on the most widely accepted scientific information availble." 179/

Dr. Thaddeus E. Prout of Johns Hopkins University believes, however, that the FDA has a responsibility to define when and how certain drugs should be used. Stricter and more specific drug licensing is necessary, he feels, to protect the consumer. In his formal statement to the

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177/ Bowen, Angela J. Oral Antidiabetics: Philosophy and Politics. Journal of the Medical Association of Georgia, Nov., 1976: 411-414.

178/ Ibid., p. 411.

179/ Ibid., p. 411.

Subcommittee, Dr. Prout wrote,

> It would appear that the most sensitive and difficult problem that is now facing the Food and Drug Administration as it relates to licensing of products is the inability to define the long-term effects of drugs that have been licensed on the basis of short-term experiments. Since this situation is unlikely to be satisfactorily changed within the near future, an investigation should be made as to whether the FDA should be required to define both the maximum drug dosage and the maximum duration of the new drugs to be licensed for use. A section in the package inset on each of the new drugs should reflect the fact that long-term safety has not been tested and state quite specifically the limitation of the dose range and the duration of therapy for which the drug has actually been tested. In brief, the package insert should more closely identify itself with its role as a protector of the consumer rather than to serve the interests of the industry. 180/

180/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 11109.

B. Policy Issues

1. Labeling. Most of the hearings witnesses believed that new labeling for oral hypoglycemic drugs was necessary. 181/ They did not agree, however, on what the label should contain or how it should be displayed. UGDP proponents have asked for a strong, clearly-worded warning about the health hazards associated with these drugs. UGDP opponents do not believe that there is sufficient evidence to warrant a strong warning. According to Dr. Schmidt, the FDA's decision to reflect the UGDP findings in a label warning "does not require that we conclude the study provides absolute proof of hazard." 182/

Quite apart from the problem of what the label should contain is the problem of how much good a package insert label would do. The insert is seen neither by the physician nor the patient. Several possibilities for circumventing this problem were discussed during the hearings.

Dr. Davidson suggested that the FDA publish a drug compendium "that uses generic names and puts all of the information at the fingertip of the physician, so he can look it up, and have responsible, scientifically creditable advice on the use of a drug." 183/ Dr. Henry T. Ricketts,

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181/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10767, 10802, 10845, 10999, 11110, 13314, 13322, 13325, 13334, 13648, 13658, 13660, 13677, 13684.

182/ Ibid., p. 13299.

183/ Ibid., p. 10845.

Professor of Medicine Emeritus at the University of Chicago Medical School, suggested that the FDA

> ...transfer the oral hypoglycemic agents to the circumscribed schedule II of dangerous drugs along with barbiturates, amphetamines, and certain narcotics. Physicians might learn that the oral agents are not exactly safe, and the requirements of BNDD prescriptions, if for dubious need, might become a salutary nuisance. 184/

Dr. Edward M. Chester testified that warnings and strong labeling by the FDA would have an effect on the use of oral hypoglycemic agents, "provided the labeling is done on the patient's drug box or bottle." 185/

2. Safety and Efficacy. Both the Food and Drug Administration and the medical community realize that no drug is either completely safe or completely effective. They have, however, been willing to accept even fairly extensive toxicity in a drug which is uniquely and unequivocally effective in saving lives or rehabilitating patients. Digitalis and levodopa are two examples of toxic drugs which are used, nevertheless, because of their effectiveness, one as a cardiac stimulator and the other as an antiparkinsonism agent. 186/

When the oral hypoglycemic drugs were first introduced into general use, it was assumed that they were at least moderately effective and certainly safe. The UGDP study has challenged these assumptions; the drugs may be neither safe nor effective.

184/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13266.

185/ Ibid., p. 13314.

186/ Ibid., p. 11008.

During the hearings, Senator Nelson questioned whether the oral agents meet the requirements for substantial evidence of safety and efficacy as written in the law. The Senator read:

> The term 'substantial evidence' means evidence consisting of adequate and well controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could be responsibly concluded by such experts that the drug would have the effect that purports to or is (sic) * represented to have, under the conditions of use prescribed, recommended or suggested in the labelling or proposed labelling thereof. 187/

Witnesses had some difficulty in answering the Senator's question. At the time these drugs were approved by the Food and Drug Administration, no significant short term deleterious side effects were detectable. 188/ Furthermore, the drugs are effective in lowering blood sugar in maturity-onset diabetics. Today, the important question is, does the strict control of blood sugar prevent or delay the serious long-term consequences of diabetes? If the answer is yes, then the possible toxicity of the oral agents represents a risk worth taking. If the answer is no, then that risk may be unjustified. However, this question has yet to be answered to the satisfaction of much of the scientific community.

Even those witnesses who accepted the findings of the UGDP study expressed the opinion that the sulfonylureas, regardless of their possible toxicity or limited effectiveness, should be kept on the market.

187/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 10805.

188/ Ibid., p. 10762

* The law actually reads, " . . . will have the effect it purports . . . " [Federal Food, Drug, and Cosmetic Act, Sec. 505 (e).]

Some cases of maturity-onset diabetes, they explained, simply cannot be controlled by diet alone. Some patients, they added, cannot take insulin because of their jobs or because of physical or mental handicaps. 189/

Would oral hypoglycemic drugs be approved for use today if they were introduced after the UGDP findings were known? At least one witness, Dr. Paul Meier of the University of Chicago, did not think so. 190/

3. Patient Information and Education. Patients have both the right and the responsibility to be adequately informed about the risks and benefits of any drugs prescribed for them. Only when provided with such information can the patient make reasoned choices about the diabetic therapy which is best for his particular situation. This concept was included in the oral hypoglycemic drug label proposed in 1975:

> The patient should be informed of the advantages and potential risks of (drug) and of alternative modes of therapy and should participate in the decision to use this drug. 191/

Labeling is one way of providing consumers with drug information, but it assumes that the patient, or at least the physician, will see the label. This is certainly not the case with package inserts, which are seen only by the pharmacist.

One solution to the problem of patient information, suggested during the hearings, is a more vigorous program of physician education. The practicing doctor needs to be better educated about the drugs she prescribes,

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189/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, pp. 10799, 10835, 11008 11100, 13266, 13295, 13296, 13302, 13303, 13315, 13319, 13646, 13656, 13660, 13673, 13677.

190/ Ibid., p. 13269.

191/ Ibid., p. 13717.

about alternative methods for controlling blood sugar, and about her obligation to educate her patients in the treatment options available to them. FDA Commissioner Schmidt testified,

> Good medical practice dictates that the patient is knowledgeable about the options of control by diet, control by insulin, and if the choice by the physician is to be the oral hypoglycemic agent, we are saying that the patient should be knowledgeable about the risks of this drug to which he may be subjected. 192/

It was also suggested during the hearings that patients taking these drugs be asked to sign a formal consent form. 193/ Dr. Philip Felig of Yale University School of Medicine did not believe that a written consent form should be required before the drugs were used, but he did feel that "the physician should document in the record of that patient, be it an outpatient record, his own office record or a hospital chart, that he has in fact discussed this matter with the patient, and the patient has been apprised of the problems, and the decision of the patient based on that." 194/

192/ The 1974-1975 Oral Hypoglycemic Drugs Hearings, p. 13303.

193/ Ibid., p. 10772.

194/ Ibid., p. 13323.

IX. CONCLUSIONS

The Food and Drug Administration has decided to base its decision on new labeling for sulfonylureas on the outcome of the UGDP data audit. The UGDP study has been considered central to the oral hypoglycemics controversy, so any decision on these drugs, the agency reasons, must rest on the validity of that study.

The controversy over the UGDP, which has received and still is receiving so much press, has obscured other facts about abult-onset diabetes and oral hypoglycemic drugs brought out during the hearings. These include:

(1) oral hypoglycemic drugs are widely overprescribed;

(2) dietary therapy and weight reduction have been neglected in the treatment of maturity-onset diabetes;

(3) insulin and dietary therapy are at least as effective as the oral agents in controlling blood sugar in the short term and probably more effective in the long term;

(4) the experience at Grady Memorial Hospital indicates that maturity-onset diabetics can be adequately controlled without oral agents and without harm to the patient;

(5) oral hypoglycemic drugs do not lower blood sugar in most patients after several years of continuous therapy; and

(6) there is no hard clinical evidence that the strict control of blood sugar prevents or delays the serious, long-term vascular and neuropathic consequences of diabetes mellitus.

The hearings did not, and indeed could not, answer the fundamental question of safety and efficacy raised by Senator Nelson in his opening statement. They did reveal, however, that:

(1) more information, both basic and clinical, is needed on oral hypoglycemic drugs;

(2) better physician and patient education in dietary management is essential; and

(3) some way of closing the "knowledge-performance" gap, of translating the results of research into improved clinical practice, should be found.

APPENDIXES

APPENDIX A

WITNESSES AT THE 1974-1975 HEARINGS

Bradley, Dr. Robert F., Director, Joslin Clinic, Boston, Mass.

Chalmers, Thomas C., M.D., President, The Mount Sinai Medical Center; Dean, Mount Sinai School of Medicine of the City University of New York.

Chayet, Neil L., Counsel, Committee for the Care of the Diabetic.

Chester, Edward M., M.D., Professor of Medicine, Case Western Reserve University, and Director, Ambulatory Medicine Teaching Clinic, Cleveland Metropolitan General Hospital.

Cornfield, Dr. Jerome, Chairman, Department of Statistics, The George Washington University, Washington, D.C.

Davidoff, Frank, M.D., Professor of Medicine and Chief of the University Hospital Medical Service, University of Connecticut Health Center, Farmington, Conn.

Davidson, John K., M.D., Ph.D., Director, Diabetes Unit, Emory University School of Medicine and Grady Memorial Hospital.

Felig, Philip, M.D., Professor and Vice Chairman, Department of Internal Medicine, Yale University School of Medicine.

Klimt, Dr. Christian R., Professor and Director, Division of Clinical Investigation, University of Maryland, Baltimore, Md.

Larner, Joseph, M.D., Ph.D., Professor and Chairman, Department of Pharmacology, and Director of the Diabetes and Endocrinology Center, University of Virginia School of Medicine.

Meier, Paul, Ph.D., Professor of Statistics, University of Chicago, Chicago, Ill.

Miller, Max, M.D., Chairman, University Group Diabetes Program, Professor of Medicine, Case Western Reserve University, Cleveland, Ohio.

Palmer, Dr. Roger, Professor of Pharmacology, University of Miami Medical School, Miami, Fla.

Palumbo, P.J., M.D., Assistant Professor of Medicine, Mayo Medical School.

Prout, Thaddeus E., M.D., Associate Professor of Medicine, The Johns Hopkins University, and Chief of Medicine, Greater Baltimore Medical Center.

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Ricketts, Henry T., M.D., Professor of Medicine Emeritus, University of Chicago Medical School.

Schmidt, Alexander M., M.D., Commissioner, Food and Drug Administration, Public Health Service, Department of Health, Education, and Welfare.

Seltzer, Holbrooke S., M.D. Chief of Metabolism at the Veterans Administration Hospital and Professor of Internal Medicine at the University of Texas, Dallas, Tx.

Sims, Ethan A.H., M.D., Professor of Medicine, College of Medicine, University of Vermont, Burlington, Vt.

Whedon, Dr. G. Donald, Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health.

White, Colin, M.D., Professor of Public Health, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn.

Zelen, Marvin, Ph.D., Professor of Statistical Science and Director, Statistical Laboratory, State University of New York at Buffalo.

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THE FEDERAL REGISTER STATEMENT, JULY 7, 1975

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 310]

[Docket No. 75N—0062]

ORAL HYPOGLYCEMIC DRUGS

Proposed Labeling Requirements and Public Hearing

The Commissioner of Food and Drugs is proposing labeling for all oral hypoglycemic drugs and announcing a legislative-type public hearing on the issues involved. Labeling for this class of drugs has been the subject of extended public controversy and legal challenge for several years. The Commissioner believes that it is now essential to resolve the outstanding issues in this matter and that it is in the interest of the public health to consider the views of all parties in achieving such resolution. Accordingly, this notice proposes class labeling for oral hypoglycemic drugs that, on the basis of all information available to the Food and Drug Administration, the Commissioner believes is consistent with the requirements of the Federal Food, Drug, and Cosmetic Act and reflects current scientific knowledge on the safety and effectiveness of these drugs.

The Commissioner invites all interested persons to submit written comments on the proposed labeling. In addition, the Commissioner's designee, the Director of the Bureau of Drugs, will conduct an oral public hearing to afford interested persons a further opportunity for the presentation of data, information, and views. In the Commissioner's judgment, the subject matter of this notice is of sufficient importance to justify the use of this additional procedure, as provided in Part 2, Subpart E, of the regulations governing the administrative practice and procedures of the Food and Drug Administration, published in the FEDERAL REGISTER of May 27, 1975 (40 FR 23025).

Interested persons may submit comments on the labeling proposed in this notice by September 5, 1975. In addition, any interested person may submit data, information, or views in writing any time within 15 days after the conclusion of the public hearing. It is the intention of the Food and Drug Administration to conduct the public hearing prior to the expiration of the time for submitting comments, and the Commissioner therefore encourages interested persons to submit their comments as soon as possible, to allow review prior to the hearing.

After consideration of all written and oral comments and all data, information, and views presented at the public hearing, the Commissioner will promulgate in the FEDERAL REGISTER a final regulation prescribing labeling for oral hypoglycemic drugs, applicable to all drug products in this class. It is anticipated that the final labeling will conform with the guidelines for labeling of prescription drugs proposed by the Commissioner on April 7, 1975 (40 FR 15392).

I. General background. The following new drug applications have been approvide for oral hypoglycemic drugs:

1. NDA 10,670, Orinase tablets containing tolbutamide; The Upjohn Co., 7000 Portage Rd., Kalamazoo, MI 49001.
2. NDA 15,500, Tolinase tablets containing tolazamide: The Upjohn Co.
3. NDA 11,841, Diabinese containing chlorpropamide; Pfizer Inc., 235 E. 42d St., New York, NY 10017.
4. NDA 13,378, Dymelor containing acetohexamide; Eli Lilly & Co., Indianapolis, IN 46206.
5. NDA 11,624, DBI tablets containing phenformin hydrochloride; Geigy Pharmaceuticals, Ardsley, NY 10502.
6. NDA 12,758, DBI–TD capsules containing phenformin hydrochloride; Geigy Pharmaceuticals.
7. NDA 17,126, Meltrol-50–100 capsules containing phenformin hydrochloride; USV Pharmaceutical Corp., 1 Scarsdale Rd., Tuckahoe, NY 10707.
8. NDA 17,127, Meltrol-25 tablets containing phenformin hydrochloride; USV Pharmaceutical Corp.
9. NDA 12,678, Tolbutamide tablets containing tolbutamide; Premo Pharmaceutical Laboratories, Inc., 111 Leuning St., South Hackensack, NJ 07606.

The class of oral hypoglycemic drugs can be grouped into two categories on the basis of chemical structure: the sulfonylurea category (represented by acetohexamide, chlorpropamide, tolazamide, and tolbutamide) and the biguanide category (represented by phenformin hydrochloride). The mode of action and adverse effects are different for these two categories of oral hypoglycemic drugs. Accordingly, separate labeling is proposed for each category of drug.

Under section 505 of the Federal Food, Drug, and Cosmetic Act, the Commissioner is responsible for assuring that all new drugs have been shown to be safe and effective for their intended uses and that their labeling is not false or misleading. Exercise of this responsibility often requires reexamination of the safety, effectiveness, or labeling of drugs previously approved. The statutory scheme contemplates that new information may require the Commissioner to prescribe changes in the labeling of a drug, to reveal newly discovered limitations on use or warn of previously unanticipated hazards. And if labeling can no longer be written to assure that the benefits of use of a drug outweigh the risks of possible harm, the Commissioner is empowered, and obligated, to withdraw marketing approval.

The Commissioner believes that information about potential risks of oral hypoglycemic drugs obtained subsequent to their initial approval for marketing requires revision of their labeling. Specifically, he believes the study of modes of treatment for adult-onset diabetes conducted by the University Group Diabetes Program requires the addition of a warning about possible cardiovascular complications associated with the use of such drugs. Because of the importance of this matter and the concerns it has generated among physicians and their patients, the Commissioner has concluded that it is appropriate to invite exploration of the issues in a public forum before reaching a final determination on the wording of the labeling, including the warning.

The scientific and legal issues relating the labeling of oral hypoglycemic drugs have been the subject of protracted public debate. To resolve the many complex questions that have been raised, it is essential that the important issues be identified and that public comment be directed to these issues. The following discussion is presented to summarize the history of the oral hypoglycemic labeling controversy, to identify the issues that have arisen during the controversy, and to explain the position of the Food and Drug Administration on these issues.

II. Origin of the labeling controversy. Although insulin and the oral hypoglycemic drugs are both effective in lowering the blood glucose level in patients with maturity-onset diabetes, it is not clear that this reduction of blood glucose has a beneficial effect on the long term vascular complications of diabetes. In an attempt to answer this question, the National Institute of Arthritis, Metabolism, and Digestive Diseases of the National Institutes of Health sponsored a long term, prospective clinical trial. The study, begun in 1961, was conducted by the University Group Diabetes Program (UGDP) in 12 university medical centers. Patients selected for the study were maturity-onset diabetics who had been diagnosed no more than 1 year prior to entry into the study and did not require insulin to remain symptom-free.

All patients were given an appropriate diabetic diet and were randomly assigned to one of four different treatment groups: (1) Fixed dose of tolbutamide (1.5 grams/day), (2) Fixed dose of insulin (10 to 16 units based on body surface area), (3) Variable dose of insulin adjusted to control the blood glucose, or (4) Placebo. Eighteen months after the study began, a fifth group was added in which the treatment was a fixed dose of phenformin hydrochloride (100 milligrams/day). Patient recruitment was completed in 1966 with a total of 1,027 patients in the entire study and approximately 200 patients per treatment group.

By 1969 the unexpected finding of a significantly higher mortality due to cardiovascular causes was present in the tolbutamide group (12.7 percent or 26 out of 204) compared to the placebo group (4.9 percent or 10 out of 205), the fixed-dose insulin group (6.2 percent or 13 out of 210), and the variable insulin group (5.9 percent or 12 out of 204). After evaluating the available data, the investigators decided to discontinue use of tolbutamide in the study because they concluded that no benefit had been shown for these patients and there was evidence that the long term use of this drug was associated with a serious side effect.

A report on the findings of the UGDP was submitted to the Food and Drug Administration in March 1970. The report

concluded that "the findings of this study provide no evidence that the combination of diet and tolbutamide therapy as described and used for mild non-insulin dependent diabetics is more effective than diet alone. Moreover, the findings suggest that tolbutamide and diet may be less effective, at least insofar as cardiovascular mortality is concerned, than diet alone or than diet plus insulin." The Food and Drug Administration reviewed the report and convened an ad hoc meeting of experts on May 21, 1970, to evaluate the findings. The report was scheduled for presentation at the annual meeting of the American Diabetes Association on June 14, 1970. The program and abstracts for the meeting of the American Diabetes Association were disseminated in May, however, and the general findings of the UGDP study became widely publicized in the press. In view of this publicity, FDA released a statement to the press on May 22, 1970, indicating that the agency agreed with the UGDP's stated conclusions and would require labeling changes for the oral hypoglycemic drugs to reflect results of the study.

In October 1970, FDA distributed a Current Drug Information Bulletin to physicians and other health professionals confirming its agreement with the stated conclusions of the UGDP study. The agency recommended that use of sulfonylurea agents be limited to those patients with symptomatic adult-onset, nonketotic diabetes who cannot be adequately controlled by diet or weight loss alone and in whom the addition of insulin is impractical or unacceptable.

The first report of the UGDP study was published in November 1970 as a supplement to Diabetes, the journal of the American Diabetes Association (ref. 1). An accompanying editorial statement representing the view of the American Diabetes Association (ref. 2) made the following therapeutic recommendations:

> The clearest indication for oral agents is diabetes of mild or moderate severity in a patient who proves to be poorly controlled with diet and who is unable or unwilling to take insulin. In adult-onset diabetes with hyperglycemia and glycosuria, symptomatic or not, and in the absence of 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 indicates that it may be safer.

A statement published at the same time by The American Medical Association Council on Drugs (ref. 3) included the following recommendations:

> 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 or 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.

In May 1971 the use of phenformin in the UGDP study also was discontinued because there was a significantly higher cardiovascular mortality in the phenformin group (12.7 percent or 26 out of 204) compared to the other treatment groups. The preliminary results with phenformin were published in August 1971 (ref. 4). An additional report by the UGDP published in November 1971 discussed the clinical implications of the UGDP study (ref. 5).

In June 1972 the Food and Drug Administration issued a Drug Bulletin outlining changes in the labeling for all sulfonylurea drugs. The Drug Bulletin stated that diet and reduction of excess weight are the foundation of therapy of diabetes mellitus, and that when the disease is adequately controlled by these measures, no other therapy is indicated. The Bulletin also stated that the sulfonylurea agents are indicated in the treatment of adult-onset, nonketotic diabetes mellitus which cannot be adequately controlled by diet and reduction of excess weight alone and when, in the judgment of the physician, insulin treatment is not feasible.

From the time the results of the UGDP study were first reported, the study was subjected to intense criticism by both clinicians and statisticians (ref. 6 through 12). The basic scientific criticisms of the study were as follows:

1. Patient selection was inappropriate in that many patients had such mild diabetes that neither oral drugs nor insulin was indicated.
2. Total mortality in the tolbutamide group was not significantly different from that in the placebo group.
3. Excess cardiovascular mortality occurred in only a few clinics.
4. Randomization was not successful; therefore, the tolbutamide group was not comparable to the other groups at the outset of the study with respect to baseline cardiovascular risk factors.
5. With the exception of the variable insulin group, patients were maintained on a fixed drug dosage, contrary to the principles of good medical practice.
6. The use of tolbutamide and phenformin in the study was terminated prematurely, i.e., before definitive results were obtained.
7. The results of the study are contradicted by the studies of Keen (ref. 13 through 15) and of Paasikivi (ref. 16).

These criticisms were in turn analyzed by representatives of the UGDP (ref. 17) and by a statistician who had served as a consultant to the UGDP (ref. 18) and were rejected as a basis for invalidating the conclusions of the UGDP study. By this time, however, a widespread belief had developed among many physicians that the UGDP study was somehow flawed in terms of its design and execution, and therefore could not serve as a proper basis for a warning to the medical profession.

Uncertainty about the scientific quality of the UGDP study has been a prominent feature of all critical commentary since 1970 and has clearly inhibited acceptance by the medical profession of the study's most troubling finding, namely, that the administration of either tolbutamide or phenformin to patients with maturity-onset diabetes was associated with an increase in cardiovascular mortality. Undoubtedly one reason many practicing physicians were surprised by and reacted critically to the findings of the UGDP study is that the reported increase in cardiovascular mortality—though statistically significant—is not of the magnitude which can be readily detected by the individual physician in the course of practice.

The Commissioner recognizes that a large number of physicians still do not accept the position of the Food and Drug Administration as expressed in the FDA Drug Bulletin, or the position of the American Diabetes Association and the American Medical Association Council on Drugs as expressed in the references cited. An outcome of this disagreement was a prolonged legal confrontation that precluded the inclusion of warnings in the labeling for oral hypoglycemic drugs similar to those appearing in the Drug Bulletin.

III. *Legal challenge to the labeling of oral hypoglycemic drugs.* In November 1970 a group of physicians known as the Committee on the Care of the Diabetic was formed to oppose the proposed warning labeling for oral hypoglycemic drugs. The group included some of the country's leading diabetologists.

In October 1971 the Committee on the Care of the Diabetic petitioned the Commissioner to rescind his position that labeling for oral hypoglycemic drugs must contain a warning of associated cardiovascular hazards. The committee maintained that the UGDP study constituted an improper basis for the agency's decision, because it had been criticized on scientific, clinical, statistical, and other grounds. The Committee on the Care of Diabetic cited "controverting data," particularly the studies of Keen et al. (ref. 13 through 15) and Paasikivi (ref. 16), which, it contended, demonstrated the safety of oral hypoglycemic therapy. The committee also insisted that labeling for these drugs must reflect a "fair balance" of scientific opinion and cite the alleged deficiencies of the UGDP study and the controversial nature of its conclusions as well as the data in controversy.

After thorough evaluation of all the materials submitted to the agency, the Commissioner formally replied to counsel for the Committee on the Care of the Diabetic on June 5, 1972. The Commissioner's letter responded to each of the criticisms raised by the committee concerning the UGDP study and the agency's position. The Commissioner reaffirmed the position of the Food and Drug Administration that an undiluted and unencumbered warning in the labeling of the oral hypoglycemic drugs regarding cardiovascular hazards was fully warranted by the available evidence.

The agency's position on labeling for these drugs was again stated in an FDA Drug Bulletin issued in May 1972. Based

on the results for phenformin reported by the UGDP in 1971, the following labeling changes were to apply to the biguanide drugs as well as the sulfonylurea drugs:

Because of the apparent increased cardiovascular hazard associated with oral hypoglycemic agents, they are indicated in adult-onset, nonketotic diabetes mellitus only when the condition cannot be adequately controlled by diet and reduction of excess weight alone, and when, in the judgment of the physician, insulin cannot be employed because of patient unwillingness, poor adherence to injection regimen, physical disabilities such as poor vision and unsteady hands, insulin allergy, employment requirements, and other similar factors.

On July 13, 1972, counsel for the Committee on the Care of the Diabetic requested a formal evidentiary hearing before the agency. The Commissioner advised the petitioners that they were not entitled to a hearing since their submission did not meet the statutory standard of "substantial evidence" and stated that the Commissioner's letters constituted final agency action.

Soon thereafter suit was filed in the United States District Court for the District of Massachusetts by a group of 178 physicians, many of them members of the Committee on the Care of the Diabetic, asking that the Food and Drug Administration be enjoined from requiring manufacturers to include a warning of associated cardiovascular hazards in their labeling for oral hypoglycemic drugs (Bradley v. Richardson), Civil No. 72-2517 M (D. Mass. 1972)). A temporary restraining order was entered by the court on the same day. A hearing on the motion for a preliminary injunction was held before Judge Campbell on August 17, 1972, and, on August 30, 1972, he denied an injunction. Judge Campbell concluded that the plaintiffs had not demonstrated a reasonable probability of prevailing on the merits since the administrative action of the Food and Drug Administration, requiring an unencumbered warning, was a reasonable exercise of its statutory duty and the potential harm to users of the drugs was greater than any harm to the manufacturers or prescribers. Judge Campbell further observed that the Food and Drug Administration labeling requirements would not preclude physicians from exercising their best clinical judgment.

The plaintiffs filed another motion for a temporary restraining order and preliminary injunction on October 17, 1972, specifically requesting that the agency be enjoined unless the drug warning was redrafted to incorporate their views concerning the interpretation of the UGDP study. The plaintiffs argued that, without such a discussion, the labeling required by the Food and Drug Administration was misleading because it failed to reveal the existence of divergent opinion among experts, contrary to the agency's own regulation, § 1.3 (21 CFR 1.3). On November 3, 1972, the District Court issued a temporary restraining order, which became a preliminary injunction on November 7, 1972, restraining the agency from implementing the labeling.

On July 31, 1973, the United States Court of Appeals for the First Circuit vacated the District Court's injunction and remanded the case to the Food and Drug Administration for its further determination. In its opinion the Court ruled that the plaintiffs failed to exhaust their administrative remedies regarding the issues presented. The Court expressed its awareness of negotiations between the parties to arrive at a mutually acceptable solution even during litigation, and also expressed its belief that the remand could well produce the most informed and responsible solution possible (483 F. 2d 410 (1st. Cir. 1973)).

In its opinion the Court of Appeals also noted apparent inconsistency between the agency's regulation on the disclosure of differences of medical opinion in § 1.3 and the substantial evidence requirements added to the Federal Food, Drug, and Cosmetic Act by the Drug Amendments of 1962. The Court directed the Commissioner to consider § 1.3 as it relates not only to the substantial evidence standard but also to the misbranding requirements of the act. The agency is revising § 1.3, by order published elsewhere at 40 FR 28581 supra in this issue of the FEDERAL REGISTER, to bring the regulation into conformity with these related provisions of the law. As revised, § 1.3 does not permit a statement of differences of opinion in required warnings in the labeling of drugs.

It should be noted that no manufacturer of oral hypoglycemic drugs has initiated proceedings challenging the Commissioner's authority to require changes in the labeling of its products, or attacking the scientific basis for the specific labeling changes that the agency proposed to require.

After the Court of Appeals vacated the preliminary injunction in July 1973, the Food and Drug Administration undertook additional discussions concerning the labeling of the oral hypoglycemic agents with interested individuals and groups. In October 1973, the Director, Bureau of Drugs, and other members of the Food and Drug Administration met with representatives of the Committee on the Care of the Diabetic, the American Medical Association, the American Diabetes Association, the National Institutes of Health, and manufacturers of hypoglycemic drugs to discuss procedures that would facilitate the issuance of appropriate labeling. Based upon the discussion and input from the agency's staff, proposed labeling revisions were circulated for comments in February 1974 to those who attend the meeting and to other interested persons. Addressees were also invited to meet with agency officials, if desired, to discuss the labeling. Four such meetings were held between March 21 and April 24, 1974. The minutes of these meetings have been placed on public display in the office of the Hearing Clerk.

The response to the proposed labeling, including comments received at these meetings, revealed continuing major differences of opinion over the scientific validity of the UGDP study and over the asserted need for "fair balance" and the acknowledgement of "controversy" in the proposed warning. In addition, the Food and Drug Administration was advised that a major outside review, described below, of the UGDP study by a committee of the Biometrics Society was near completion.

The agency therefore decided to postpone implementation of the warning until this review was published. Since the UGDP study was the basis for the proposed warning, the Commissioner believed that this independent review of the statistical validity of the study should be available to all interested persons before taking definitive action. The review by the committee of the Biometrics Society required extensive reanalysis of the data in the UGDP study and was not published until February 10, 1975 (ref. 19). A more detailed report of the UGDP on phenformin was also published recently (ref. 20).

The Commissioner believes that sufficient time has passed to have permitted all interested persons to study these reports. Since no major new information in regard to the UGDP study is anticipated, the Commissioner believes it is now essential to effect all labeling changes that are appropriate and necessary on the basis of the UGDP study.

On June 11, 1975, and June 18, 1975, representatives of the Food and Drug Administration met with representatives of the Committee on the Care of the Diabetic to discuss late drafts of the Indications and Warnings sections of the labeling proposed in this notice. The representatives of the Committee on the Care of the Diabetic included one of the plaintiffs in Bradley v. Weinberger and the plaintiffs' attorney. The purpose of these meetings was to engage in good faith negotiation in an attempt to resolve outstanding issues in conformity with the intent of the Court of Appeals. Memoranda of these meetings and of subsequent phone calls and drafts of labeling discussed at the meetings are on file in the office of the Hearing Clerk.

IV. *Review of biostatistical issues by the Committee of the Biometrics Society.* The UGDP study was subjected to intense adverse criticism (ref. 6 through 12) largely on the basis of its design and the statistical analysis of the results. For this reason, the National Institute of Arthritis, Metabolism, and Digestive Diseases, which financed the UGDP study, sought an independent reveiw of the study. In 1972 a contract was awarded to the Biometrics Society, an international organization of biostatisticians, to make an in-depth assessment of the scientific quality of the UDGP study, particularly the biometric aspects of the design, conduct, and analysis of the trial, and a similar assessment of other controlled trials involving oral hypoglycemic agents. A committee of six members was selected to undertake this task. The committee visited the UGDP coordinating center and two of the clinical centers to study methods used in the trial, reviewed published criticisms of the UGDP study

in detail, interviewed both critics and supporters of the study, and made new analyses from the original data.

On the basis of this in-depth review, the Biometrics Society committee commented as follows on the major criticisms of the UGDP study:

1. The criticism that patient selection was inappropriate was considered to be "largely irrelevant to the primary issue raised by the critics," viz., the validity of the evidence pointing to excess mortality in the tolbutamide- and phenformin-treated groups. The committee argued that even "if it could be shown that the study group contained some non-diabetics * * * [a] drug found toxic in such subjects would not likely be counted safe for persons with well documented mild diabetes either."

2. With respect to the criticism that total mortality in the tolbutamide group was not significantly different from that in the placebo group, the committee concluded that this criticism "has some weight (although we do not interpret it as a criticism of the action of the UGDP) and that the toxic effect of the oral hypoglycemics cannot be affirmed with the certainty that would be present if total mortality were significantly different."

3. In response to the criticism that excess mortality occurred in only a few clinics, the committee presented calculations of the data to take account of the number of patients treated in each clinic and the duration of their treatment and concluded that "the excess mortality is not in fact confined to a few clinics and that this particular criticism should not be taken to detract from the interpretation of the UGDP findings."

4. The contention that randomization was not successful was studied in detail by the committee which identified "a puzzling anomaly concerning the distribution of the two sexes to the four treatment groups within clinics." The committee reviewed the randomization procedure in detail and examined the log books containing records of the allocation of each patient. The committee's report reads: "We were not able to find an assignable cause for the surprising allocation of the sexes to treatments but have no reason to think that the study has been compromised by a breakdown in the randomization of patients to the treatment groups. Because of the imbalance of sexes in the treatment groups in some clinics, however, allowance for this has been made in our analysis." The committee went on to analyze the data by several different statistical approaches, including those used originally by the UGDP investigation. The committee concluded: "Our findings * * * take into account the differences between centers and the differences in length of treatment, as well as the baseline variables. They support the view of Cornfield [ref. 18] that there is no evidence that the baseline differences arising from the randomization contributed in any important way to the finding of adverse effect from tolbutamide."

5. The criticism that the oral hypoglycemic drugs were given in fixed dosage was rejected by the committee, with respect to conclusions regarding toxicity, as follows: "It is true that the use of a fixed dose of drug, which was also the approach adopted by Feldman et al. [ref. 21] and Keen and Jarrett [ref. 14], limits the generalization about therapeutic effects, but since the dose of tolbutamide is about equal to the average recommended for therapeutic use, an evaluation of its possible toxic effect is highly relevant."

6. Concerning the criticism that the use of tolbutamide and phenformin was terminated prematurely, the committee acknowledged that "It would have been easier to interpret the findings if there were more data on mortality." The committee also recognized, however, the ethical issues raised by continuing these drugs in the study and concluded: "We do not criticise the UGDP investigators for having made the decision when they did. Nevertheless, the result of that decision is to leave us with some residual uncertainty about the meaning of the findings, a point that is well understood by the UGDP investigators themselves."

7. In considering the criticism that the results of the UGDP study are contradicted by the studies of Keen (ref. 13 through 15) and of Paasikivi (ref. 16), the committee analyzed these studies in detail. With respect to the data of Keen and his colleagues, they concluded that, in their ongoing prospective study, neither cardiovascular mortality nor total mortality in the tolbutamide group is significantly different from that in the placebo group. Because of imperfections in the randomization process and in the maintenance of blinding, and because of the preliminary nature of the data obtained to date, the committee concluded that "the provisional data that Dr. Keen has kindly sent us * * * do not throw doubt on the UGDP findings in regard to deaths from cardiovascular causes." In regard to the Paasikivi study, which appeared to show a beneficial effect of tolbutamide on mortality in the first year in patients who survived a first myocardial infarction, the committee concluded: "This study neither confirms nor contradicts the UGDP findings, as the population under consideration was not one of maturity-onset diabetics, and the patients taking tolbutamide had been exposed to a relatively small dose for a shorter time than that applied in the UGDP study." The studies of Feldman et al. (ref. 21) and of Tzagournis and Reynertson (ref. 22) were also briefly reviewed by the committee. Their conclusion was that in neither study has a sufficient number of deaths yet occurred to permit meaningful interpretation of results.

In addition to evaluating these criticisms of the UGDP study, the Biometrics Society committee conducted extensive new analyses of the UGDP data, taking into account the effect of various baseline variables and cardiovascular risk factors. These analyses confirmed that cardiovascular mortality was increased in the tolbutamide group. This increase was statistically significant in females, especially in women over the age of 53 but not in males. An important finding was that the highest death rate occurred in the group of patients who adhered most closely to the tolbutamide regimen and did not have their dose modified. Also when the analysis was conducted according to an approach called the survival modeling method, which takes into account the proportion of time each patient received the assigned medication, women in the tolbutamide group had a statistically significant increase in both cardiovascular and total mortality. This does not mean that the study necessarily showed the drug to carry less risk in males. On this point the committee concluded: "The data do not support the same conclusions for men, but one possible reason is that the smaller number of patients in the male group results in lack of sensitivity to detect differences of moderate magnitude."

In the final section of its report, the Biometrics Society committee summarized its conclusions:

> Although we have concerned ourselves almost entirely with issues related to the possible toxicity of tolbutamide, we wish to point out that one of the valuable aspects of the completed UGDP trial will be the provision of data on the long term treatment of adult-onset diabetes with insulin. It is already clear that the benefits from this treatment are not dramatic, and the only worthwhile information about them will have to come from the relatively precise methods of a controlled clinical trial. In this sphere, the UGDP trial has no competitor * * *
>
> On the question of cardiovascular mortality due to tolbutamide and phenformin, we consider that the UGDP trial has raised suspicions that cannot be dismissed on the basis of other evidence presently available.
>
> We find most of the criticism levelled against the UGDP findings on this point unpersuasive. The possibility that deaths may have been allocated to cardiovascular causes preferentially in the groups receiving oral therapy exists, and, in view of the 'nonsignificance' of differences in total mortality, some reservations about the conclusion that the oral hyperglycemics [sic] are toxic must remain. Nonetheless, we consider the evidence of harmfulness moderately strong. The risk is clearly seen in the group of older women * * * Whether it affects all subgroups of patients cannot be decided on the basis of the available data, owing to the small number of deaths involved in these subgroups * * *
>
> In conclusion, we consider that in the light of the UGDP findings, it remains with the proponents of the oral hyperglycemics [sic] to conduct scientifically adequate studies to justify the continued use of such agents.

V. *Recent additional information on safety of oral hypoglycemic drugs.* The more detailed report on the results of the phenformin study was published recently by the UGDP (ref. 20). In addition to the higher mortality from all causes and from cardiovascular causes observed in the phenformin-treated group compared to the other treatment groups, evidence was presented that phenformin therapy resulted in increased blood pressure levels and heart rate, thus suggesting possible mechanisms by which this drug might influence cardiovascular mortality.

Recently, additional reports relating to the safety of oral hypoglycemic drugs have appeared:

1. At hearings before the Subcommittee on Monopoly of the Select Committee on Small Business, U.S. Senate, on January 31, 1975, Dr. P. J. Palumbo reported that a retrospective study of diabetic patients treated at the Mayo Clinic suggests that survival was lower in those patients treated with oral hypoglycemic agents, compared to those patients treated with insulin. The full study has not yet been published.

2. A retrospective study of diabetic patients treated at the Joslin Clinic, reported in a doctoral thesis (ref. 23), can be interpreted as providing results that are consistent with those of the UGDP. This study has not yet appeared in the medical literature.

3. A positive inotropic effect, i.e., increased force of muscular contraction, of sulfonylurea agents on the heart muscle has been demonstrated (ref. 24 and 25). The increased oxygen requirement resulting from such an effect could have a deleterious effect in patients with coronary artery disease. Limited animal studies also suggest that the sulfonylurea agents may affect the excitability of heart muscle (ref. 25), which could predispose the heart to develop abnormal rhythms, particularly in the presence of a decreased oxygen supply.

4. Results from a study on the chronic effects of tolbutamide in the rhesus monkey by R. W. Wissler et al. (FDA contract 72-114) indicate there is an increased frequency and severity of atherosclerotic lesions in the coronary arteries of the tolbutamide-fed monkeys compared to the control monkeys (ref. 26). The final report of this study is under review.

While neither of the two epidemiological studies is a prospective clinical trial such as the UGDP study, the preliminary reports indicate that further information casting doubt on the safety of the oral hypoglycemic drugs may be forthcoming. And, although the animal findings cannot be considered necessarily relevant to the issue of excess cardiovascular mortality in diabetic patients, they indicate that sulfonylureas may have potentially adverse effects on the cardiovascular system of certain animals which can be detected by appropriate pharmacological and toxicological tests.

In addition to these reports, two critiques of the Biometrics Society committee report have recently been published (ref. 27 and 28).

VI. *Discussion of proposed labeling for oral hypoglycemic drugs.* The judgment of the Commissioner that changes must be made in the labeling of the oral hypoglycemic drugs to reflect the findings of the UGDP study is well known from previously published statements. The Commissioner is therefore proposing labeling in this notice for public comment and scheduling a public hearing to receive additional data, information, and views. After consideration of all materials submitted, the Commissioner will publish final labeling for oral hypoglycemic drugs in the FEDERAL REGISTER.

The warning proposed in this labeling for oral hypoglycemic drugs is based primarily on a thorough review and evaluation of the UGDP study. In proposing the overall labeling, the Commissioner has also carefully considered:

1. Published reviews, criticisms, and rejoinders to criticism of the UGDP study.
2. Other scientific and clinical investigations of the oral hypoglycemic agents.
3. The advice of experts.
4. Comments submitted to the agency by interested persons.

The Commissioner reaffirms his conclusion that the UGDP study is an adequate and well-controlled clinical trial, which is the most extensive and detailed examination of long term administration of hypoglycemic agents yet undertaken. Although the study has shortcomings, which might be expected in any clinical trial of this complexity, 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 a warning be issued whenever there is sufficient evidence from controlled or uncontrolled studies to believe that a drug may be hazardous or carry a risk and that such warning is necessary for safe and effective use of the drug by physicians and patients. The Federal Food, Drug, and Cosmetic Act provides no standard for the amount or character of scientific evidence required for the issuance of a warning. The decision to require a warning is a matter of judgment which must be made in light of both the available scientific evidence and the opinion of experts who interpret that evidence. The Commissioner believes that the UGDP study is a validly conducted trial and accepts the opinion of the Biometric Society committee and other experts that the increased cardiovascular mortality found in this trial to be associated with these drugs cannot reasonably be attributed to scientific shortcomings in the study. Under those circumstances, a clear warning is necessary even though a residual uncertainty over the correctness of the study may be present. Warnings may properly be required on the basis of evidence that falls short of conclusive proof.

In conformity with Food and Drug Administration policy that warnings must be presented in unambiguous terms without disclaimers or qualifications that would undermine or destroy their usefulness, there is no mention in the proposed warning of other studies involving the oral hypoglycemic drugs. The mention of studies in which increased cardiovascular mortality was not found would serve only to encumber the warning and would therefore not be consistent with revised § 1.3. Comments concerning the principle of an unencumbered warning, which have been received and considered in conjunction with the proposed revision of § 1.3 published in the FEDERAL REGISTER of September 16, 1974 (39 FR 33229), are addressed in the final regulation published at 40 FR 58581, supra.

The proposed warning does, however, contain a statement acknowledging the controversy that exists over the interpretation of the UGDP study and states that, in spite of this, the UGDP findings provide adequate scientific basis for a warning. The purpose of this statement is to emphasize clearly the basis for the warning. Comments on specific wording in the proposed warning are invited by this notice. The Commissioner advises, however, that he does not intend to reopen consideration of the principle of an unencumbered warning which is embodied in the final regulation relating to § 1.3.

The Commissioner concludes that, from the standpoint of patient safety, it is prudent to apply the possible increased risk of cardiovascular mortality for tolbutamide and phenformin to other sulfonylurea and biguanide drugs in view of the similarities in chemical structure and mode of action for members within each of these two categories. This position was endorsed by the Endocrinology and Metabolism Advisory Committee of the FDA at its meeting on June 28, 1971, but additional comment at this time would also be appropriate.

The Commissioner also concludes that a patient population exists for which these drugs, properly labeled, can be considered as safe and effective. Marketing therefore may continue. The Commissioner is proposing, however, that this patient population be limited to patients with maturity-onset diabetes whose symptoms or blood glucose level cannot be controlled by diet alone and who cannot take insulin for one or more of the reasons identified in the labeling. This restriction in labeling has been opposed in the past on the ground that it interfered with the practice of medicine. The

Commissioner recognizes that drug labeling impacts on the practice of medicine. For this reason the Food and Drug Administration has an obligation to ensure that drug labeling is as correct and accurate as possible and meets the statutory standard of describing the conditions of use under which the drug may be considered safe and effective. Those limitations on use that properly derive from a known hazard or potential risk must, in the interest of safety, be included in drug labeling. This principle is stated in the proposed regulations on prescription drug labeling (published in the FEDERAL REGISTER of April 7, 1975 (40 FR 15392)), time for coment on which has been extended to August 6, 1975, by notice published in the FEDERAL REGISTER of June 11, 1975 (40 FR 24909).

The Commissioner proposes the appended labeling for oral hypoglycemic agents of the sulfonylurea and biguanide categories as labeling providing the essential information for the safe and effective use of these drugs. Comments addressed to any portion of the labeling will be considered.

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28. O'Sullivan, J. B. and R. B. D'Agostino, "Decisive Factors in the Tolbutamide Controversy," *Journal of the American Medical Association*, 232:825–829, 1975.

VII. *Notice of public hearing.* The Commissioner concludes that, to permit maximum public participation in the development of labeling requirements for oral hypoglycemic drug products, a public hearing shall be held to provide an opportunity for interested persons to present data, information, and views on the proposed labeling. This public hearing is ordered pursuant to § 2.400(a) (21 CFR 2.400(a)) and shall be conducted in accordance with the procedures established in Subpart E of Part 2 of the regulations. The Commissioner has designated J. Richard Crout, M.D., Director, Bureau of Drugs, to be the presiding officer at such hearing, to be held August 20, 1975, beginning at 9 a.m. in Conference Rm. E, Parklawn Bldg., 5600 Fishers Lane, Rockville, MD 20852.

Interested persons who wish to make an oral presentation at the hearing shall file a written notice of appearance with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852 by close of business August 6, 1975. The notice of appearance shall state the approximate amount of time requested by the person for presentation. It shall also give the telephone number of the person to be contacted regarding the schedule for presentation. Individuals and organizations with common interests are strongly urged to consolidate or coordinate their presentations because of the limitations of time.

By August 11, 1975, the Food and Drug Administration will communicate by telephone with each person who requested an opportunity to be heard, regarding the time his or her oral presentation is scheduled to begin and the amount of time allocated for his or her presentation. The Food and Drug Administration may require joint presentations by persons sharing common views. The Food and Drug Administration will prepare a hearing schedule, listing the participants and the time allotted to each, which shall be filed with the Hearing Clerk and a copy mailed to each participant.

The hearing will be transcribed. Any interested person may, consistent with the orderly conduct of the meeting, also record or otherwise make his or her own transcript of the meeting. Each participant may use the allotted time however he or she desires, consistent with decorum and order, and may present written data, information or views for inclusion in the record of the hearing. Any person who desires to submit an advance written statement may do so in quintuplicate to the Hearing Clerk. All written comments and statements submitted before August 15, 1975, will be reviewed by the presiding officer prior to the hearing, so that full repetition at the hearing will be unnecessary. A participant may be accompanied by any number of additional persons.

If a participant is not present when his or her presentation is scheduled to begin, the participants following will be taken in order. An attempt will be made to hear any scheduled participant who misses his assigned time at the conclusion of the hearing. Other interested persons attending the hearing who did not request an opportunity to speak will be

given an opportunity to make oral presentations at the conclusion of the hearing to the extent that time permits.

The presiding officer, as well as any other Food and Drug Administration employee serving with him as a panel, may question any participant during or at the conclusion of his presentation. No other persons attending the hearing may question a participant. The presiding officer may allot additional time to any participant if he concludes that it is in the public interest, but may not reduce the time allotted to anyone.

The record of the hearing will remain open until September 5, 1975, for the submission of any additional written statements or comments regarding oral presentations made at the hearing.

No written submission, or any portion thereof, made in response to this notice shall be received or held in confidence. The administrative record of this rule making proceeding shall consist of all relevant FEDERAL REGISTER notices and the documents to which they refer, all written submissions made in response to this notice, and the transcript of the oral hearing made by the Food and Drug Administration. The administrative record of the proceeding shall be made available for public examination.

VIII. *Proposed regulation for the labeling of oral hypoglycemic drugs.* Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502.505, 701(a), 52 Stat. 1050–1053, as amended, 1055 (21 U.S.C. 352, 355, 371(a))) and under authority delegated to him (21 CFR 2.120), the Commissioner proposes that Part 310 of Subchapter D of Title 21 of the Code of Federal Regulations be amended by adding a new § 310.510 as follows:

§ 310.510 Labeling for oral hypoglycemic drugs.

(a) An adequate and well-controlled clinical trial (the University Group Diabetes Program study) has indicated that there appears to be an increased risk of cardiovascular mortality associated with the administration of tolbutamide and of phenformin (oral hypoglycemic drugs of the sulfonylurea and biguanide categories, respectively) to maturity-onset diabetic patients as compared to treatment with diet alone or diet plus insulin. The Commissioner concludes that in view of the great similarities in chemical structure and mode of action for drugs within each of these two categories, it is prudent from a safety standpoint to consider that the possible increased risk of cardiovascular mortality for tolbutamide and phenformin also applies to other sulfonylurea and biguanide drugs. Therefore, the labeling for oral hypoglycemic drugs shall describe properly the conditions for their use and include a warning concerning the possible increased risk of cardiovascular mortality associated with such use, as set forth in paragraphs (b) and (c) of this section.

(b) Labeling for oral hypoglycemic drugs of the sulfonylurea category shall be as follows:

DESCRIPTION

(Trade name, established name) is an oral blood-glucose-lowering drug of the sulfonylurea category. It is a white, crystalline compound, formulated as a tablet for oral administration. (Manufacturer to add structural formula and other appropriate information.)

ACTIONS

Administration of (drug) appears to lower the blood glucose initialy by stimulating the release of insulin from the pancreas; the effect is thus dependent on functioning beta cells in the pancreatic islets. The mechanism by which (drug) lowers blood glucose during long term administration has not been clearly established. Many patients who at first demonstrate an adequate glucose-lowering effect with a sulfonylurea agent subsequently prove to be no longer satisfactorily responsive, i.e., secondary failure may occur.

(Manufacturer to supply information about:

1. Absorption.
2. Metabolism and excretion.
3. Plasma half-life and the effect of hepatic or renal impairment on blood levels, metabolism, and excretion.
4. Peak and duration of glucose-lowering effect, indicating the duration of effect relative to the class of sulfonylurea agents, e.g., shortest acting, longest acting, etc.
5. Mechanism of drug interaction with agents that impair or potentiate drug effect.)

INDICATIONS

(Drug) is indicated to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet alone and in whom insulin cannot be used because of patient unwillingness, erratic adherence to the injection regimen, poor vision, physical or mental handicap, insulin allergy, employment requirements, or other similar factors.

(Drug) may also be used to lower blood glucose in asymptomatic patients whose blood glucose elevation cannot be controlled by diet alone and in whom insulin cannot be used for any of the above reasons. In considering the use of (drug) in asymptomatic patients, it should be recognized that whether or not controlling the blood glucose is effective in preventing the long term cardiovascular or neural complications of diabetes is an unanswered scientific question.

The use of (drug) may be associated with an increased risk of cardiovascular mortality as compared to diet alone or diet plus insulin; see WARNINGS. For this reason, it should be used only when the advantages in the individual patient justify the potential risk. The patient should be informed of the advantages and potential risks of (drug) and of alternative modes of therapy and should participate in the decision to use this drug.

The foundation of therapy in the obese maturity-onset diabetic is caloric restriction and weight loss. Proper dietary management alone is often effective in controlling the blood glucose and eliminating symptoms of polydipsia and polyuria. Use of (drug) must be considered by both the physician and patient as a treatment *in addition* to diet and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint.

Many patients who are initially responsive to oral hypoglycemic drugs become unresponsive or poorly responsive over a period of time, usually 1 to 5 years. (Drug) should be given only to patients demonstrated to be responsive to it; see DOSAGE AND ADMINISTRATION for discussion of secondary failure. Short term administration of (drug) may be sufficient during periods of transient loss of control.

Concomitant Therapy with a Biguanide. (Drug) may be used in conjunction with phenformin to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet and maximum recommended doses of either drug alone and in whom insulin cannot be used for any of the reasons cited above.

In considering the use of concomitant therapy, it should be noted that both a sulfonylurea drug (tolbutamide) and a biguanide drug (phenformin) have been reported to be associated with increased cardiovascular mortality; see WARNINGS. In addition, phenformin can produce lethal lactic acidosis in some patients. Thus the use of (drug) in association with phenformin carries a greater risk than the use of (drug) alone.

If a judgment is made that (drug) and phenformin are to be used together in a particular patient, it should be established that the patient is responsive to both drugs. This may be accomplished either by a trial of each drug separately or by adding the second drug and then tapering the dosage of the first, observing for diminished control of blood glucose. Once the need for both drugs is established, the desired control of blood sugar may be obtained by adjusting the dose of either drug. The possibility of hypoglycemia should be anticipated and appropriate precautions taken. See package insert for phenformin hydrochloride for CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

(Drug) is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.
2. Diabetic ketoacidosis, with or without coma. Such patients should be treated with insulin.

WARNINGS

SPECIAL WARNINGS ON CARDIOVASCULAR MORTALITY

(This subsection of labeling to be boxed, set in boldface type, and placed at the beginning of WARNINGS section of labeling.)

The administration of oral hypoglycemic drugs may be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.

This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with maturity-onset nonketotic diabetes. The study involved 1,027 patients who were randomly assigned to one of five treatment groups (Diabetes, 19 (supp. 2): 747–830, 1970; Diabetes, 24 (supp. 1): 65–184, 1975).

The UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) or diet plus a fixed dose of phenformin (100 milligrams per day) had a rate of cardiovascular mortality approximately twice that of patients treated with diet alone or diet plus insulin. Total mortality was increased in both the tolbutamide- and phenformin-treated groups, but this increase was statistically significant only for phenformin. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide adequate scientific basis for this warning.

Although only one drug in the sulfonylurea category (tolbutamide) and one in the biguanide category (phenformin) were included in this study, it is prudent from a safety standpoint to consider that this result may also apply to other oral hypoglycemic drugs in these categories, in view of the close similarities in mode of action and chemical structure among the drugs in each category.

(Drug) should be used in preference to insulin only in patients with maturity-onset diabetes whose symptoms or blood glucose level cannot be controlled by diet alone and only when the advantages in the individual patient justify the potential risk; see INDICATIONS. The patient should be informed of the advantages and potential risks of (drug) and of alternative modes of therapy and should participate in the decision to use this drug.

(Drug) is not effective in patients with juvenile diabetes or insulin-dependent diabetes at any age. Such patients should be treated with insulin. The concomitant long term use of insulin and (drug) in an individual patient is, in view of the potential risk of increased cardiovascular mortality with (drug), less safe on a benefit-risk basis than the use of insulin alone.

The effectiveness of any oral hypoglycemic drug, including (drug), in lowering blood glucose to a desired level decreases in a large number of patients as the drug is administered over a period of months or years, in part because the patient's blood glucose tends to rise over time and in part because of diminished responsiveness to the drug. This phenomenon is known as secondary failure to distinguish it from primary failure in which the drug is ineffective in an individual patient at the time of its initial administration. See DOSAGE AND ADMINISTRATION.

Renal or hepatic insufficiency may cause elevated blood levels of (drug) and increase the risk of serious hypoglycemic reactions.

Pregnancy: (Data and interpretation related to reproduction and teratology studies to be supplied by manufacturer).

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. Neonatal hypoglycemia has been reported more frequently following use of the longer-acting agents. If (drug) is used during pregnancy, it should be discontinued (time period to be supplied by manufacturer) before the expected delivery date.

Precautions

Hypoglycemia: All sulfonylurea drugs are capable of producing severe hypoglycemia. Particularly susceptible are elderly patients, patients with impaired hepatic or renal function, patients who are debilitated or malnourished, and patients with adrenal or pituitary insufficiency. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, or when more than one glucose-lowering drug is used.

(To be inserted for chlorpropamide only:) Because of the long half-life of chlorpropamide, patients who become hypoglycemic during therapy require careful supervision of the dose for at least 3 to 5 days, during which time frequent feedings are essential. It may be necessary to hospitalize such patients and give intravenous glucose.

Certain drugs may potentiate the hypoglycemic action of (drug), including phenylbutazone, oxyphenbutazone, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. See ACTIONS. When such drugs are administered to a patient receiving (drug), the patient should be observed closely for hypoglycemia.

Loss of Control of Blood Sugar: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a loss of control may occur. At such times it may be necessary to discontinue (drug) and administer insulin.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other oral diuretics, corticosteriods, and (to be supplied by manufacturer). When such drugs are administered to a patient receiving (drug), the patient should be carefully observed for loss of control.

Pseudo-albuminuria (tolbutamide only). Urine containing a tolbutamide metabolite may give a false positive reaction for albumin if the acidification-after-boiling test is used, because this procedure causes the metabolite to precipitate as flocculent particles. Use of the sulfosalicylic acid test circumavents this problem.

Adverse Reactions

Hypoglycemia. See PRECAUTIONS.

Gastrointestinal Reactions. Cholestatic jaundice may occur rarely; (drug) should be discontinued if this occurs.

Gastrointestinal disturbances, e.g., nausea, epigastric fullness, and heartburn are the most common reactions, occurring in (manufacturer to supply estimate of incidence). They tend to be dose related and may disappear when dosage is reduced.

Dermatologic reactions. Allergic skin reactions, e.g., pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occur (manufacturer to provide estimate of incidence). These may be transient and may disappear despite continued use of (drug); if skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported.

Hematologic Reactions. Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported.

Metabolic Reactions. Hepatic porphyria, disulfiram-like reactions (manufacturer to supply further details).

(To be inserted for chlorpropamide only:)

Endocrine Reactions. On rare occasions (drug) has caused a reaction identical to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. The features of this syndrome result from excessive water retention and include hyponatremia, low serum osmolality, and high urine osmolality.

Dosage and Administration

There is no fixed dosage regimen for the management of diabetes mellitus with (drug) or any other agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically:

a. To determine the minimum drug dosage that will lower the blood glucose adequately.

b. To detect primary failure, i.e., inadequate lowering of blood glucose when the drug is first used, even though dose has been raised to the maximum level recommended; and

c. To detect secondary failure, i.e., loss of adequate blood-glucose-lowering response after an initial period of effectiveness. (Drug) should be discontinued, with careful monitoring of blood glucose at least annually to be certain that (drug) is continuing to lower the blood glucose.

Short term administration of (drug) may be sufficient during periods of transient loss of control.

(Manufacturer to supply the following details of dosage for each sulfonylurea

1. Usual starting dose.
2. Maximum dose.
3. Dose beyond which a response is usually not seen if patient has not already had some response.
4. Usual maintenance dose.
5. Dosage interval, with reasons, e.g., avoid GI tolerance, short half-life of drug, etc
6. Caution regarding dosage in elderly.)

How Supplied

(To be supplied by manufacturer.)

(c) Labeling for oral hypoglycemic drugs of the biguanide category shall be as follows:

Description

(Trade name, established name) is an oral blood-glucose-lowering drug of the biguanide category. It is a white, crystalline, water-soluble compound, formulated as (to be supplied by firm) for oral administration. Manufacturer to add structural formula and other appropriate information.)

Actions

The mechanism of action of phenformin is not established but its ability to cause increased peripheral glucose uptake in vitro appears to be related to its inhibition of cellular oxidative processes. It does not stimulate insulin production. Many patients who at first demonstrate an adequate glucose-lowering effect with (drug) subsequently prove to be no longer satisfactorily responsive, i.e., secondary failure may occur.

(Manufacturer to supply information about:

1. Absorption.
2. Metabolism and excretion.
3. Plasma half-life and the effect of hepatic or renal impairment on blood levels, metabolism, and excretion.
4. Peak and duration of glucose-lowering effect.
5. Mechanism of drug interaction with agents that impair or potentiate drug effect.)

Indications

Identical to sulfonylurea label, except for substitution of the following section relating to concomitant therapy:

Concomitant Therapy. Phenformin may be used in conjunction with a sulfonylurea to control symptoms due to hyperglycemia in patients with maturity-onset nonketotic diabetes mellitus whose symptoms cannot be controlled by diet and maximum recommended doses of either drug alone and in whom insulin cannot be used for any of the reasons cited above.

In considering the use of concomitant therapy, it should be noted that both phenformin and a sulfonylurea drug (tolbmutamide) have been reported to be associated with increased cardiovascular mortality; see WARNINGS. Thus the use of phenformin in association with a sulfonylurea may carry a greater risk than the use of phenformin alone.

If a judgment is made that phenformin and a sulfonylurea are to be used together in a particular patient, it should be established that the patient is responsive to both drugs. This may be accomplished either by a trial of each drug separately or by adding the second drug and then tapering the dosage of the first, observing for diminished control of blood glucose. Once the need for both drugs is established, the desired control of blood sugar may be obtained by adjusting the dose of either drug. The possibility of hypoglycemia should be anticipated, and appropriate precautions taken. See package insert for the appropriate sulfonylurea for

CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

(Drug) is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.

2. A history of lactic acidosis.

3. Disease states associated with hypoxemia including cardiovascular collapse and acute myocardial infarction.

4. Severe renal disease.

5. Alcoholism.

6. Diabetic ketoacidosis with or without coma. Such patients should be treated with insulin.

WARNINGS

SPECIAL WARNING ON CARDIOVASCULAR MORTALITY

(Identical to boxed, boldface sulfonylurea labeling.)

(Drug) is not adequate therapy in patients with juvenile diabetes or insulin-dependent diabetes at any age. Such patients should be treated with diet and insulin. The concomitant long term use of insulin and (drug) in an individual patient is, in view of the risk of increased cardiovascular mortality with (drug), less safe on a benefit-risk basis than the use of insulin alone.

The effectiveness of any oral hypoglycemic drug, including (drug), in lowering blood glucose to a desired level decreases in a large number of patients as the drug is administered over a period of months or years, in part because the patient's blood glucose tends to rise over time and in part because of diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient at the time of its initial administration. See DOSAGE AND ADMINISTRATION.

Lactic Acidosis. There have been numerous reports of lactic acidosis in patients receiving phenformin. Lactic acidosis is an often fatal metabolic acidosis characterized by elevated blood lactate levels, an increased lactate-to-pyruvate ratio, and decreased blood pH. Azotemia ranging from mild to severe is present in most of the reported cases of lactic acidosis. Azotemia can result from dehydration, and some patients developing lactic acidosis associated with azotemia have had normal serum creatinine levels when properly hydrated. The following specific precautions should be observed when administering phenformin:

a. Impairment of renal function increases the risk of lactic acidosis. Renal function tests, such as serum creatinine, should be performed prior to phenformin therapy and at least annually thereafter. Phenformin should not be used in patients with impaired renal function, e.g., serum creatinine over 1.5 milligrams/100 milliliters, except in extraordinary circumstances.

b. Cardiovascular collapse (shock), congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and also may cause prerenal azotemia. Use of phenformin in patients particularly prone to develop such conditions must be carefully considered and the risks weighed against possible benefits. When such events occur in patients on phenformin therapy, the drug should be discontinued promptly.

c. Gastrointestinal disturbances are the most common adverse reactions to phenformin therapy. These symptoms must be distinguished from the symptoms of developing lactic acidosis. Anorexia and mild nausea are common side effects of phenformin, particularly upon initiation of therapy. Nausea, vomiting, malaise, or abdominal pain may herald the onset of lactic acidosis. The patient should be instructed to notify the physician immediately at the onset of any of these gastrointestinal symptoms or of hyperventilation. Phenformin should be withdrawn until the situation is clarified by determination of serum electrolytes and ketones, blood glucose, and, if indicated, blood pH, lactate, and pyruvate levels.

d. Lactic acidosis has a significant mortality and, when suspected, must be treated promptly by discontinuing phenformin and giving bicarbonate infusions and other appropriate therapy even before the results of lactate determinations are available. Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis in the absence of ketonuria and ketonemia, uremia, and methanol or salicylate poisoning.

e. The physician should use special caution after initiating phenformin therapy, after increasing the drug dosage, and in circumstances that may cause dehydration leading to impaired renal function.

f. Alcohol is known to potentiate the effect of phenformin in elevating blood lactate levels, and patients should be warned against excessive alcoholic intake while receiving phenformin.

g. Impaired hepatic function has been associated with some cases of lactic acidosis. Particular caution must be observed when administering (drug) to patients with hepatic disease.

Pregnancy: (Data and interpretation related to reproduction and teratology studies to be supplied by manufacturer).

PRECAUTIONS

Hypoglycemia: Hypoglycemia is unusual in patients receiving (drug) alone, but may occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or when more than one hypoglycemic drug is used.

(Manufacturer to supply paragraph on potentiating drugs.)

Loss of Control of Blood Sugar: Identical to sulfonylurea labeling.

Change in Clinical Status of Previously Controlled Diabetic: A diabetic patient previously well-controlled on phenformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose, and, if indicated, blood pH, lactate, and pyruvate levels. Acidosis of either form necessitates withdrawing phenformin and initiating other appropriate corrective measures.

Starvation Ketosis: This must be differentiated from insulin-deficient ketosis and is characterized by ketonuria with little or no glucosuria and relatively normal blood glucose levels. This may result from excessive dosage of phenformin or insufficient carbohydrate intake.

ADVERSE REACTIONS

Hypoglycemia: See PRECAUTIONS.

Gastrointestinal Reactions: Gastrointestinal disturbances such as anorexia, nausea, vomiting, and diarrhea are the most common adverse reactions (manufacturer to supply frequency) and are dose related. These symptoms must be distinguished from the prodromata of lactic acidosis. See WARNINGS section for discussion of lactic acidosis. They may also cause dehydration and prerenal azotemia, which require discontinuation of the drug until renal function is again normal. Phenformin should be discontinued if vomiting occurs. An unpleasant metallic taste is a warning signal of impending gastrointestinal disturbances.

Dermatologic Reactions: (Manufacturer to supply data, including estimate fo incidence.)

Miscellaneous Reactions: Fatigue and weakness. Anorexia, nausea, and vomiting may occur in association with the intake of alcohol.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of diabetic mellitus with (drug) or any other agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically:

a. To determine the minimum drug dosage that will lower the blood glucose adequately.

b. To detect primary failure, i.e., inadequate lowering of the blood glucose when the drug is first used, even though dose has been raised to the maximum level recommended.

c. To detect secondary failure, i.e., loss of adequate blood-glucose-lowering response after an initial period of effectiveness. Drug should be discontinued with careful monitoring of blood glucose at least annually to be certain that (drug) is continuing to lower the blood glucose.

Short term administration of (drug) may be sufficient during periods of transient loss of control.

(Manufacturer to supply the following details of dosage:

1. Usual starting dose.

2. Maximum dose.

3. Dose beyond which a response is usually not seen if patient has not already had some response.

4. Usual maintenance dose.

5. Dosage interval, with reasons, e.g., avoid GI intoleranse, short half-life of drug, etc.

6. Caution regarding dosage in elderly.)

HOW SUPPLIED

(To be supplied by manufacturer.)

(d) Each holder of an approved new drug application for an oral hypoglycemic agent shall submit a supplement to his application under the provisions of § 314.8(d) of this chapter to provide for labeling as described in paragraphs (b) and (c) of this section. The labeling in such supplement shall be identical in wording to the labeling in paragraphs (b) or (c) of this section where precise wording is specified, shall provide information on each of the points where wording is delegated to the manufacturer, and shall contain no additional or extraneous information. Such supplement shall be submitted within 10 days after (effective date of the final regulation). Any oral hypoglycemic drug with labeling not in compliance with this section and shipped into interstate commerce after (60 days after effective date of the final regulation) shall be subject to regulatory action.

Interested persons may, on or before September 5, 1975, submit to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, written comments regarding this proposal. Comments shall be filed in quintuplicate and shall be identified with the Hearing Clerk docket number found in the document heading. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 1, 1975.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

[FR Doc.75-17530 Filed 7-3-75;8:45 am]

APPENDIX D

WARNING LABEL FOR ORAL HYPOGLYCEMIC DRUGS ISSUED MAY, 1972

ATTACHMENT J

FDA Drug Bulletin May 1972, Final Labeling Approved for Oral Hypoglycemic Drugs

[From FDA Drug Bulletin May, 1972]

FINAL LABELING APPROVED FOR ORAL HYPOGLYCEMIC DRUGS

The most recent labeling for the sulfonylurea drugs and for phenformin, approved by the Food and Drug Administration, provides that these 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.

The labeling includes a SPECIAL WARNING which says:

"Diet and reduction of excess weight are the foundations of initial therapy of diabetes mellitus. When the diseases is adequately controlled by these measures, no hypoglycemic drug therapy is indicated. Because of the apparent increased cardiovascular hazard associated with oral hypoglycemic agents, they are indicated in adult-onset, non-ketotic diabetes mellitus only when the condition cannot be adequately controlled by diet and reduction of excess weight alone, and when, in the judgment of the physician, insulin cannot be employed because of patient unwillingness, poor adherence to injection regimen, physical disabilities such as poor vision and unsteady hands, insulin allergy, employment requirements, and other similar factors."

This labeling and therapeutic regimen for diabetes mellitus are consistent with the therapeutic recommendations of the American Diabetes Association and the Council on Drugs of the American Medical Association, with which FDA consulted on the evaluation of the University Group Diabetes Program (UGDP) study.

The long-term UGDP study provided the basis for the labeling. That study suggested that the use of the sulfonylurea drug tolbutamide and the biguanide drug phenformin were associated with a greater incidence of cardiovascular mortality than diet alone, or than insulin plus diet.

Although the specific sulfonylurea drug studied by UGDP was tolbutamide (Orinase), the conclusions apply equally to all sulfonylureas—Diabinese, Dymelor, Orinase and Tolinase—because of their close chemical relationship. Of the biguanides, only DBI–TD was studied by UGDP, but the conclusions apply to DBI and Meltrol as well.

Further studies are being undertaken to shed additional light on the role of sulfonylureas and phenformin in the management of diabetes mellitus.

The "indications" section of the labeling approved recently by FDA for all oral hypoglycemic drugs says:

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.

Because of the increased cardiovascular hazard which appears to be associated with oral hypoglycemic agents, the drugs should be used only after full consideration of the special warning.

APPENDIX E

ORAL HYPOGLYCEMIC DRUG CERTIFICATION DATA, 1973-1977

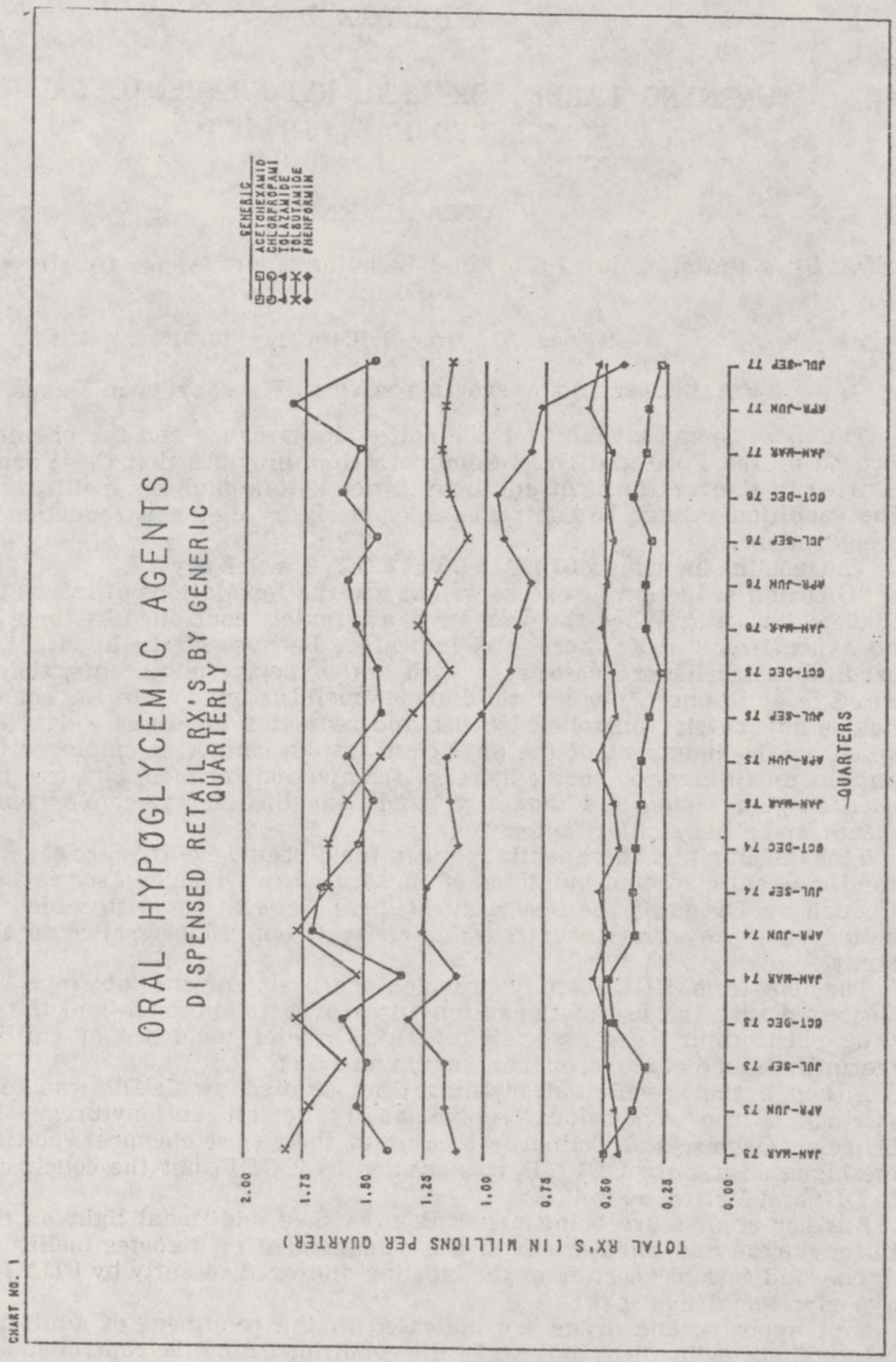

CHART NO. 1

APPENDIX F

ORAL HYPOGLYCEMIC DRUG CERTIFICATION DATA
THIRD QUARTER, 1977

ORAL HYPOGLYCEMIC DISTRIBUTION

1977

THIRD QUARTER
(JULY AUGUST SEPT)

	N	*R*	*T**
ACETOHEXAMIDE	74	201	275
A.DYMELOR(LILLY)	74	201	275
B.WRITTEN GENERICALLY	0	0	0
CHLORPROPAMIDE	475	990	1465
A.DIABINESE(PFIZER)	474	986	1460
B.WRITTEN GENERICALLY	1	4	5
TOLAZAMIDE	133	395	528
A.TOLINASE(UPJOHN)	133	395	528
B.WRITTEN GENERICALLY	0	0	0
TOLBUTAMIDE	266	876	1142
A.ORINASE(UPJOHN)	266	876	1142
B.WRITTEN GENERICALLY	0	0	0
PHENFORMIN	84	345	429
A.DBI(GEIGY)	6	24	30
B.DBI-TD(GEIGY)	75	311	386
C.MELTROL(USV)	3	10	13
B.WRITTEN GENERICALLY	0	0	0

*
N=NEW RX FILLED
R=RX REFILLED
T= TOTAL RX FILLED

ADD (000) TO ALL FIGURES

APPENDIX G

ORDER OF THE SECRETARY SUSPENDING APPROVAL,
NEW DRUG APPLICATIONS FOR PHENFORMIN

SUMMARY SECTION

UNITED STATES

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

OFFICE OF THE SECRETARY

In re:

New Drug Applications

for Phenformin

NDA 11-624
NDA 12-752
NDA 17-126
NDA 17-127

ORDER OF THE SECRETARY

SUSPENDING APPROVAL

July 25, 1977

This proceeding was initiated by a petition filed by the Health Research Group (HRG), a consumer advocacy group concerned with health matters. It grows out of extensive scientific investigation and concern over the possible association between use of phenformin and lactic acidosis, a metabolic disorder which is frequently fatal. This is one of two proceedings which have as their ultimate objective the removal of this drug from general marketing.

II. SUMMARY

Diabetes is a major health problem directly affecting at least 5,000,000 Americans. Most people suffering from this disease face the probability of major complications and a shortened life span. In 1976, almost two million of these diabetics were estimated to be taking oral drugs, including about 385,000 patients who were taking phenformin.

Phenformin is used to control blood sugar levels in patients with adult-onset diabetes. As commonly distributed, phenformin allows diabetics who use it to control their condition with fewer dietary restrictions or to delay the time when they must begin taking insulin. In general, its effectiveness diminishes over time, usually within two to three years, and in many patients insulin therapy ultimately must be initiated.

By October 1976, FDA had received reports of a total of 190 phenformin patients who were identified as having suffered from lactic acidosis -- most of these cases occurring between 1974 and 1976. This volume of cases in a voluntary reporting system, which tends to underreport adverse drug reactions, was of sufficient concern that at this time, the FDA Bureau of Drugs referred the subject to its Endocrinology and Metabolism Advisory Committee. Following presentations by FDA personnel and a phenformin manufacturer, the Advisory Committee concluded that an unequivocal association existed between the use of phenformin and the occurrence of lactic acidosis and that there wase sufficient evidence to indicate a causal relationship, although the mechanism of causality was not clear. The Committee unanimously recommended removal of the drug from the market.

Subsequent to this recommendation the Bureau of Drugs finished its own review of the scientific information and also concluded that a clear association, strongly indicating causality, had been established between the use of phenformin and the occurrence of lactic acidosis. Because lactic acidosis is frequently fatal, and because alternative effective therapies are available for treatment of diabetes, the Bureau determined that the risks of phenformin therapy outweighed its possible benefits. Therefore, on May 6, 1977,

the Bureau commenced formal legal proceedings to withdraw approval of phenformin under the procedures prescribed in the law. Since then, both manufacturers have formally requested a full evidentiary hearing on the issues of fact in this matter.

Prior to the commencement of formal proceedings by the Bureau of Drugs, the HRG filed a petition contending that the drug phenformin constituted an "imminent hazard to the public health" within the meaning of the Federal Food, Drug and Cosmetic Act, and requesting that the Secretary immediately suspend approval. The issue presented by this petition is whether the continued use of phenformin constitutes so serious a threat to public health that the drug should be removed from the general market immediately pending completion of procedures to determine whether to remove it permanently.

Upon receiving the HRG petition, I requested FDA Commissioner Kennedy and his scientific colleagues in the Bureau of Drugs to evaluate it and advise me on the proper response. FDA held a public hearing on May 13, 1977, to allow interested parties to comment on the petition before me so that I would have the benefit of the views of all interested parties. Information and views were presented by the manufacturers of phenformin and by diabetes experts

including physicians, representatives of the American Diabetes Association, American Medical Association, and the Committee on the Care of the Diabetic.

On June 27 and July 18, 1977, Commissioner Kennedy forwarded to me the Bureau's detailed analysis of the use and risks of phenformin, accompanied by a discussion of the available options and a set of recommendations.

The Federal Food, Drug and Cosmetic Act requires that all "new drugs" must be subject to a new drug application (NDA) "approved" by the Secretary before they may be shipped in interstate commerce. To obtain approval for an NDA, a manufacturer must prove, inter alia, that such a drug is safe.

The burden of establishing safety of a new drug remains, at all times, on the manufacturer. Whenever new evidence appears that an approved new drug may be or is unsafe, FDA is required to remove the drug from the market. The Act establishes two procedures for removing an approved drug from the market: "withdrawal" and "suspension". The ordinary administrative procedure required to "withdraw" approval of an NDA requires notice to the manufacturer, an opportunity for a full evidentiary hearing before a hearing officer, and a decision by the Commissioner based on the hearing record. These procedures usually require at least six months, and often take much longer, sometimes years.

The elaborate procedural protections against improvident withdrawals emphasize the importance of the immediate suspension provision available under the Act. Established in 1962, this summary procedure permits the Secretary to act promptly to suspend approval of an NDA temporarily, and thereby remove the drug from the market, if it represents an "imminent hazard to the public health." The Secretary must provide the manufacturer with an expedited hearing on whether the drug should be permanently removed, while the drug is off the market as a result of the suspension. This special authority is vested solely in the Secretary of Heath, Education, and Welfare. Under either procedure, a manufacturer is offered an opportunity for a full evidentiary hearing (whether or not expedited) before a drug may be permanently removed from the general market.

After examining the Act, the legislative history and pertinent court decisions, I concluded that the following factors should be weighed in determining whether approval of an NDA should be suspended on the ground that continued use of the drug will constitute an imminent hazard to the public health:

A. The severity and likelihood of the harm that could be caused by the drug during the completion of customary administrative proceedings to withdraw the drug permanently from the general market.

B. The likelihood that, after the customary administrative process is completed, the drug will be withdrawn from the general market.

C. The risk to patients currently taking the drug that might be occasioned by the immediate removal of the drug from the general market, taking into account the availability of other therapies and the steps necessary for patients to adjust to these other therapies.

D. The availability of other approaches to protect the public health.

The adverse drug reaction involved in this proceeding is life-threatening. About one-half of the 245 cases of phenformin-related lactic acidosis reported to FDA by June 1977 under the voluntary reporting system were fatal. Little serious dispute exists that the percentage of fatalities associated with lactic acidosis is high. Such a high incidence of fatal side effects plainly represents the type of hazard that Congress intended the Secretary to consider -- with the utmost care -- as one of those potentially extreme situations in which summary suspension of an NDA would be appropriate. Moreover, the evidence in the record indicates a substantial likelihood of a causal connection between use of phenformin and lactic acidosis.

An accurate assessment of the incidence of lactic acidosis among phenformin patients represents a critical factor in deciding whether phenformin's NDAs should be suspended immediately. Because conflicting testimony had been presented on this point, the Bureau made an intensive review of publicly available information from four distinct sources: the

manufacturers, nationwide data from several countries, a prospective controlled study in a group of university-based medical centers, and reports from individual hospitals. This analysis for the first time assembled and compared data based on clinical experience in a number of countries, and it provides a convincing picture of the very serious hazards associated with the use of phenformin.

Data submitted by CIBA-Geigy included 395 cases of lactic acidosis reported between 1964 and 1976. Norway discontinued marketing of phenformin after four cases of fatal drug-associated lactic acidosis were reported in a three-year period (1974-76). Finland observed 18 cases of lactic acidosis, half of them fatal, in a five-year period (1972-76). Sweden reported 19 fatal and nonfatal cases in 1974, seven in 1975, and one in 1976. The national health authorities in New Zealand conducted a survey of phenformin-related cases of lactic acidosis in that country between 1973 and 1975, and found 24 cases of which at least six were fatal. The University Group Diabetes Program in the United States monitored 204 diabetics treated with phenformin and 823 treated with other therapy; three phenformin-treated patients developed lactic acidosis, while none of the patients on other therapies did. In Australia, data collected at one hospital over a two-year period showed 14 cases. In a single United States hospital in a 2-year period (1970-71), eight cases of lactic acidosis occurred among phenformin users.

After reviewing these reports of lactic acidosis in phenformin users, the Bureau calculated that the "range of reasonable estimates is perhaps between 0.25 and 4 cases per 1,000 phenformin users per year . . .," and that the overall mortality rate in these reported cases was approximately 50%. Thus, the estimated incidence of death due to lactic acidosis in phenformin users is 0.125 to 2 deaths annually per 1,000 patients.

While a number of drugs can cause death if administered in excess dosage,, very few drugs approved for marketing in the U.S. carry a risk of death when used appropriately under the approved conditions of labeling. Even those few drugs known to cause fatal reactions when used properly carry a much lower risk of death than phenformin. Death due to penicillin anphylaxis occurs, for example, in an estimated 0.02 patients per 1,000 treated. Death from thromboembolism due to oral contraceptives occurs in approximatley 0.01 to 0.03 patients per 1,000 treatment years. Cases of aplastic anemia from chloramphenicol, many of which are fatal, occur in an estimated 0.025 cases per 1,000 courses of therapy. Thus,the estimated incidence of death due to lactic acidosis in phenformin users is on the order of 5 to 80 times higher than that associated with these other drugs.

Currently an estimated 336,000 diabetics are being treated with phenformin (a decline from the 385,000 in 1976). On this basis, the Bureau estimates that between four and 60 patients will die each month from phenformin-

700 users of phenformin will suffer fatal lactic acidosis during the coming year. Even if one uses the incidence estimate based upon the cases voluntarily reported to the manufacturers (0.1 cases annually per 1,000 patients), given a mortality rate of 50%, there will still be a death every three weeks that phenformin remains available for use at current levels. This represents a minimum of approximately 17 deaths a year.

In short, based on the evidence in the record and the statistics of past experience, phenformin appears to have an incidence rate of fatalities associated with its general use that is far higher than has been regarded as acceptable for any other drug approved for use in the United States for a broad patient population.

I recognized that many of the incidence calculations reflected in the above statistics involve estimates and assumptions. But I also appraised this evidence against the following background:

-- The relationship between phenformin use and lactic acidosis has been a source of concern to the medical profession for more than a decade and has been a subject of many investigations.

-- Several major diabetes treatment centers in hospitals in the United States have discontinued the use of the drug in the light of the high fatality rate of phenformin-related lactic acidosis.

-- At least two countries, Norway and Canada, have removed phenformin from the market because of deaths due to lactic acidosis.

-- The statistical evidence from all available sources consistently shows a high rate of phenformin-induced lactic acidosis.

-- The FDA, which is experienced in interpreting and analyzing incidence figures for adverse reactions, has examined those statistics and concluded that the incidence figures are scientifically valid.

I find a very substantial likelihood that the incidence rate of fatal lactic acidosis among phenformin users is many times higher than FDA has thought acceptable in the past. Based on existing safety standards, I further find a very substantial likelihood that continued use of phenformin by a large population of patients will result in an unacceptably high rate of death and that therefore the severity and likelihood of harm to the public are very great.

Based on my review of the present record and particularly of the data reflecting the incidence of phenformin-associated lactic acidosis, I find it likely that phenformin will be withdrawn permanently from the general market. I find it unlikely that the manufaturers will be able to sustain their burden, under the Act, of showing that phenformin is safe which is necessary to keep the drug on the market.

I have given careful consideration to the potential harm that could result to diabetics from removing phenformin as a treatment for this disease. While commonly used, phenformin is not a life-saving drug. It is not a permanent treatment because its effectiveness diminishes over time. Further, it is not an essential drug for the care of diabetes except in unusual cases discussed below. Several diabetes clinics in major hospitals, including clinics at the Emory University School of Medicine and Grady Memorial Hospital in Atlanta, Georgia; Case Western Reserve University, in Cleveland, Ohio; the University of Pennsylvania Hospital, and Yale-New Haven Hospital, have discontinued the use of phenformin entirely.

Given the daily need for medication, a failure to plan for an orderly transition from phenformin therapy to other therapies could threaten the well-being of many diabetics. This potential for harm can, however, be eliminated by an open and cooperative effort on the part of FDA, the manufacturers, the professions of medicine and pharmacy, and other appropriate groups, and I am requesting their cooperation. I am also directing that the Commissioner establish a 90-day transitional phase-out period to ensure, through this cooperative effort, that patients currently receiving phenformin can be transferred in a safe, orderly, and consistent manner to other therapies.

A small patient population does exist, however, that may be particularly benefited by the continued availability of phenformin to them. These are persons who fall into one of two categories: (1) those who have difficulty administering insulin to themselves because of mental or physical infirmity and have no one available to assist them; or (2) those such as crane operators or truck drivers whose occupations are such that they cannot be allowed to run the risk of a hypoglycemic reaction to insulin (a shock reaction that may cause unconsciousness), and who also meet all of the following conditions:

(a) they have symptoms in addition to high blood sugar, such as excessive water intake and urine volume, changing vision, or genital and urinary tract infections;

(b) they cannot use sulfonylureas (the only other oral anti-diabetic drug), either because those drugs alone do not control their symptoms or because they cannot tolerate those drugs;

(c) they do not have other conditions such as kidney impairments or cardiovascular diseases which increase the risk of lactic acidosis; and

(d) their symptoms are controlled by a treatment program that includes phenformin.

The number of such patients can be assumed to range from perhaps several hundred to several thousand.

FDA advised me that without a change in the present distribution methods phenformin could not effectively be

restricted to the relatively small number of patients whose special circumstances justify exposure to the risks of taking phenformin.

I, therefore, directed Commissioner Kennedy to initiate prompt discussions with the manufacturers and professional associations to devise a voluntary controlled distribution system which will assure the continued availability of the drug to only the limited population for whom the benefits outweigh the risk. If such a distribution system can be established, the suspension could be modified. Alternatively, phenformin could be made available on a restricted basis to appropriate patients under the investigational new (IND) authority of the Federal Food, Drug, and Cosmetic Act.

As a first step toward the creation of a limited distribution system, Commissioner Kennedy, other responsible officials of the Department, and I are meeting today with a group of leading doctors, pharmacists, and representatives of the drug companies most affected by this action. I believe that the manufacturers and the drug and health cae professionals will cooperate with FDA to devise a mutually acceptable distribution program that will meet the needs of these relatively few patients.

I concluded that, as currently labeled and distributed, the drug phenformin constitutes an "imminent hazard to the public health", and suspend approval of all new drug applications for this drug, under the Federal Food, Drug, and Cosmetic Act, pending completion of FDA proceedings to withdraw the drug permanently from the general market.

APPENDIX H

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APPENDIX I

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APPENDIX J

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