UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

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MEETING NO. 72

+ + +

Friday, March 26, 1999

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The Advisory Committee met in Versailles Rooms I, II, and III, Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, at 8:00 a.m., Henry G. Bone, III, M.D., Chairman, presiding.

PRESENT:

HENRY G. BONE, III, M.D., Chairman

KATHLEEN REEDY, Executive Secretary

JULES HIRSCH, M.D., Member

D. ROGER ILLINGWORTH, M.D., Ph.D., Member

ROBERT A. KREISBERG, M.D., Member

MARK E. MOLITCH, M.D., Member

PRESENT (Continued):

GLENN BRAUNSTEIN, M.D., FDA Consultant

JOSE FRANCISCO CARA, M.D., FDA Consultant

COLLEEN A. COLLEY, Pharm.D., FDA Consultant

SAUL GENUTH, M.D., FDA Consultant

ROBERT MARCUS, M.D., FDA Consultant

MARIA I. NEW, M.D., FDA Consultant

RICHARD J. HAMMES, R.Ph., M.S., B.C.N.P.,
Consumer Representative

JAMES H. LEWIS, M.D., Guest Expert

LEONARD B. SEEFF, M.D., Guest Expert

NORMAN FLEISCHER, M.D., Guest Expert

REBECCA W. KILLION, Guest Expert

JAMES M. BILSTAD, M.D., FDA Representative

DAVID GRAHAM, M.D., M.PH., FDA
Representative

SOLOMON SOBEL, M.D., FDA Representative

ROBERT TEMPLE, M.D., FDA Representative

JEFFREY MILLER, M.D., Public Comment

ROBERT BUSCH, M.D., Public Comment

STEVEN V. EDELMAN, M.D., Public Comment

PATRICK J. BOYLE, M.D., Public Comment

ANNE PETERS, MN.D., Public Comment

RAMACHANDIRAN COOPPAN, M.D., Public Comment

PRESENT (Continued):

TOM HALSTEAD, Public Comment

MEHMOOD KHAN, M.D., Public Comment

THOMAS J. MOORE, Public Comment

JOSE LOUIS BAUTISTA, M.D., Public Comment

DANIEL EINHORN, M.D., FACP, FACE, Public Comment

WILLIAM CLARK, M.D., Public Comment

VINCENT PEARSON, Pharm.D., Public Comment

SIDNEY M. WOLFE, M.D., Public Comment

STEPHEN CLEMENT, M.D., Public Comment

GERALD FAICH, M.D., MPH, Sponsor Representative

PHILIP HOME D.M., D.Phil., Sponsor Representative

MARK PIERCE, M.D., Ph.D., Sponsor Representative

PAUL WATKINS, M.D., Sponsor Representative

RANDALL WHITCOMB, M.D., Sponsor Representative

ROBERT ZERBE, M.D., Sponsor Representative

C-O-N-T-E-N-T-S

C-O-N-T-E-N-T-S (Continued)

P-R-O-C-E-E-D-I-N-G-S

(8:10 a.m.)

CHAIRMAN BONE: Good morning, everyone. I'm Dr. Henry Bone. I'm calling to order the 72nd meeting of the Endocrinologic and Metabolic Drugs Advisory Committee.

The topic today is a discussion of experience since approval for marketing of the benefits and risks of troglitazone, and also there will be some discussion of triple therapy involving this agent with sulfonylurea and metformin in the treatment of Type 2 diabetes mellitus.

The first item will be to go around the front table to introduce the people who are here from the agency and from the Advisory Committee, and I think we'll just begin with that. Perhaps we'll start at the far right with Dr. Temple.

DR. TEMPLE: Thanks. I'm Bob Temple. I'm CDER's Associate Director for Medical Policy.

DR. BILSTAD: Jim Bilstad, Office of Drug Evaluation 2.

DR. SOBEL: Saul Sobel, the Metabolic and Endocrine Drug Division.

DR. GRAHAM: David Graham, a medical epidemiologist in the Office of Postmarketing Drug

Risk Assessment in CDER.

DR. SEEFF: I'm Leonard Seeff from the NIDDK and the VA.

DR. LEWIS: I'm James Lewis from Georgetown University. I direct hepatology there.

DR. ILLINGWORTH: Roger Illingworth, Oregon Health Sciences University, Portland, Oregon.

MR. HAMMES: Dick Hammes, pharmacist, University of Wisconsin.

DR. GENUTH: Saul Genuth, Case Western Reserve University.

DR. BRAUNSTEIN: Glenn Braunstein, Cedars-Sinai Medical Center, Los Angeles.

CHAIRMAN BONE: Henry Bone, Michigan Bone and Mineral Clinic at St. John Medical Center in Detroit.

MS. REEDY: Kathleen Reedy, Food and Drug Administration.

DR. MOLITCH: Mark Molitch, Northwestern University in Chicago.

DR. NEW: Maria New, Cornell University Medical College.

DR. KREISBERG: Bob Kreisberg, Birmingham, Alabama.

DR. COLLEY: Colleen Colley, VA Medical

Center in Portland, Oregon.

DR. FLEISCHER: Norman Fleischer, Director of Endocrinology at the Diabetes Research Center at Albert Einstein College of Medicine.

DR. MARCUS: Robert Marcus, Stanford University and the Veterans' Affairs Medical Center in Palo Alto.

MS. KILLION: Rebecca Killion. I'm a Type 2 diabetic. I'm here as a patient representative.

DR. HIRSCH: Jules Hirsch, Rockefeller University.

Henry, I can't see you. So send up a rocket if you want me to comment or something.

CHAIRMAN BONE: All right. Perhaps during the discussion we can arrange to have the projector moved.

All right. Thank you all.

The next item is the presentation of the meeting statement by Kathleen Reedy, the Executive Secretary.

MS. REEDY: Conflict of interest statement for the Endocrinologic and Metabolic Drugs Advisory Committee, March 26th, 1999.

The following announcement addresses the issue of conflict of interest with regard to this

meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 United States Code 208(b), full waivers have been granted to Dr. Mark Molitch, Dr. Glenn Braunstein, Dr. Henry Bone, and Dr. Saul Genuth.

Copies of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, located in Room 12A30 of the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to FDA's invited guests, there are reported interests which we believe should

be made public to allow the participants to objectively evaluate their comments. Dr. Norman Fleischer would like to disclose for the record that he serves as a member of Parke-Davis' Speakers Bureau. In addition, in 1998, Dr. Fleischer attended a meeting on Rezulin sponsored by Parke-Davis.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRMAN BONE: Thank you.

The next item on the agenda is the remarks upon background and purpose by Dr. Bilstad, Director of the Office of Drug Evaluation 2.

DR. BILSTAD: Good morning. First I would like to address the question why we are having this Advisory Committee meeting.

First slide.

There continue to be reports of serious hepatotoxicity despite labeling recommendations for frequent monitoring of liver function tests, which currently are recommended at baseline and monthly thereafter for the first eight months.

In addition, recently we have become aware of a number of reported cases that appear to have had

a very rapid course, which raises questions about the adequacy of frequent monitoring to prevent liver failure.

Next.

On the other hand, troglitazone has a different mechanism of action from other approved drugs to treat diabetes, and it is effective in helping to control hyperglycemia in Type 2 diabetics.

We want to review with the Committee the experience with the drug since it was approved for marketing, and we are asking for the Committee's views on the assessment of the drug's overall benefits and risks.

Next.

I would like to briefly review some aspects of the regulatory history for troglitazone. The NDA was received by FDA in August of 1996, and it was designated as a priority application because of its different mechanism of action.

It was presented to this Committee on December -- in December 1996. At that time, hepatotoxicity was discussed only to a limited extent.

The Committee recommended approval for use in Type 2 diabetics who were currently taking insulin, but were not adequately controlled.

Next.

Less than two weeks after the 1996 Advisory Committee meeting, a safety update was submitted to the FDA that included additional cases of hepatotoxicity. The drug was approved for marketing in the end of January 1997, and the labeling indication was as discussed at the Advisory Committee, for patients who were taking insulin but were judged not to be adequately controlled.

Next.

The labeling at the time of initial approval included hepatotoxicity information and the precautions and the adverse reaction sections based on the information in the safety update. The labeling stated that 2.2 percent of patients in the controlled clinical trials had an AST or ALT greater than three times the upper limit of normal.

The labeling also reported that two patients had developed jaundice while taking troglitazone which subsided after the drug was stopped.

Next.

Efficacy supplements were submitted by the sponsor to expand the indications. In August 1997, labeling was approved that allowed for concomitant use

of troglitazone with the sulfonylurea drug to improve glycemic control.

At the same time, the labeling indication was also expanded to include monotherapy with troglitazone, provided that the patients had not previously been well controlled on sulfonylureas.

Next.

The first fatalities associated with hepatotoxicity were reported to the FDA by Parke-Davis in October 1997. Shortly thereafter, the labeling was changed to include a bolded warning about the possibility of hepatic failure, including death.

Recommendations for monitoring liver function tests were also included in the labeling. The recommendation at that time was that they be checked during the first one to two months of therapy and every three months thereafter during the first year.

Next.

Additional reports of serious hepatotoxicity were received, and in December 1997, a boxed warning about the possibility of hepatic failure and death was added to the beginning of the labeling.

The recommendations for monitoring liver function tests were also changed. Testing was

recommended when therapy with troglitazone was started, to be repeated every month for the first six months, and every two months for the remainder of the first year.

Next.

The last labeling change was made in July of last year. At that time the monthly monitoring of liver function testing was extended from six months to eight months.

In addition, the statement was added that troglitazone therapy should not be started if the ALT was great than one and a half times the upper limit of normal. A statement was also included in the boxed warning that if an ALT was obtained in the range of one and a half to two times greater than the upper limit of normal, LFTs should be repeated within a week and then repeated weekly until the levels returned to normal.

The primary issue that we are bringing to the Committee is for your consideration of the potential overall benefits and risks for the labeled indications, i.e., for the combination with either sulfonylurea drugs or with insulin and for monotherapy.

We are, however, also asking the Committee

for comments on the proposed indication for combination with sulfonylureas and metformin.

We also want to raise the issue of how successful the labeling recommendations for monthly monitoring during the first eight months of therapy are in reducing the cases of liver failure.

Dr. David Graham from FDA's Office of Postmarketing Drug Risk Assessment will later address a number of issues relating to hepatotoxicity.

I would also like to point out that we recognize the difficulties in attempting to define and quantitate the potential long-term benefits of drugs used in the treatment of diabetes. The sponsor will be addressing potential benefit issues with troglitazone, as well as issues relating to hepatotoxicity.

That concludes my opening remarks, and I look forward to the presentations today and to the discussion on certainly this very difficult and challenging subject.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Bilstad.

In a moment we'll start the open public hearing section of the meeting. As I usually like to

remark, it's a very American characteristic to have such an opportunity in deliberations of a committee advising a drug registration authority, and I look forward to the remarks that will be made by each of the people who are scheduled to talk.

I will ask the people to stay within the time that they've agreed on with Kathleen Reedy, the Executive Secretary, and I'll give you a little signal at four minutes like this, and please. As I said, she's discussed this with you I know.

She has a comment to make first of all about the materials.

MS. REEDY: Because of the number of people who requested to speak in the open public hearing, letters that were submitted for the open public hearing are printed and available, and everyone at the table has them in their folder, and there are a stack of them where you picked up the agendas if you would like to have a copy, but there are about six or eight letters and another six or eight letters that respond to the citizens petition, which you'll hear more about.

CHAIRMAN BONE: Thank you very much.

The first speaker in the open public hearing -- with this large number of speakers, it is

Dr. Jeffrey Miller of Thomas Jefferson University Hospital in Philadelphia, and if we can have people sort of waiting when they're next so that we don't have too much time in between just waiting for people to come up to the podium, I think that will help us move along.

Dr. Miller.

And I will say: would any of the open public hearing speakers who have an interest that could be regarded as a financial interest please state that as well? We've asked that everyone be candid about this.

Thank you very much. Dr. Miller, please.

DR. MILLER: Thank you, Dr. Bone.

Ladies and gentlemen, I am on the Speaker's Bureau of Parke-Davis, Eli Lilly, NovoNordisk, Knorr (phonetic) Pharmaceuticals, Bayer Pharmaceuticals, to mention quite a few.

I am here representing the ten million-plus diabetics who in this country suffer from the epidemic of obesity. I'm here in my private capacity with no other inclination.

The problem, as I foresee it, in these overweight diabetics who die at the death rate of about 500 people per day is that contrary to what we

currently believe -- and I've done a little survey in my own practice, which is probably the largest single handed endocrine-diabetes practice in the City of Philadelphia -- is ask my patients a simple question. If you don't take care of yourself as a diabetic, what will happen to you?

And the uniform answer is, "Doctor, I will die as a result of kidney failure, blindness, or limb amputation."

Unfortunately, that is not the reality. That is some five percent of total deaths. Seventy-five percent of diabetics die as a result of the scourge of cardiovascular disease, and the onus on us as treating health care providers is to provide these people with what I've termed heart healthy. We need to prolong their life spans by allowing them to be free of atherosclerosis, and it my belief, based on a number of scientific publications, including the Paris prospective study, that in order to prevent cardiovascular disease, we need to go beyond simple issues that we address every day, that is, beyond blood glucose, beyond hypertension, and beyond hypolipidemic indices.

We need to look at the beta cell. We need to look at the entity of endogenous insulin production

as being potentially involved in this whole atherosclerotic process, and this, I believe, is with this new group of compounds, I believe, the most exciting category of compounds to be around in the last 40 years, the thyozolic endiones or the glutazones, as I call them, have really come to the fore.

These are agents that in numerous peer reviewed articles provide cardiovascular protection in terms of improved vascular reactivity, decreased platelet aggregation, decrease in triglycerides, improvement in lipoprotein a, improvement in overall LDL characteristics from an atherogenic to a non-atherogenic potential, to name but a few.

This agent, I believe, has gone beyond simple diabetes management, has gone beyond blood glucose. Diabetes is no longer a glucose disorder. To myself as a practicing clinician, educated, diabetes is a vascular disease, and in order to cut down the thrust of this disorder on the vascular system, I have relied very heavily on the insulin sensitizers, first the bioguanides, the midformin, and more recently the even more powerful beta sulresta (phonetic), troglitazone.

Life is an analysis of risk and benefits.

On Wednesday night just before going to be, I listened to the President talking about Yugoslavia and was talking about the risk of American lives in terms of the benefits that we can get out of this war.

The same with our daily lives in terms of medicine. It's a risk-benefit analysis. I unfortunately recently heard about a patient, a young lady on antithyroid agents for Grace hypothyroidism who succumbed to agranulocytosis. That was a risk-benefit analysis on the part of her physician to treat her with antithyroid agents rather than radioiodine which has no deaths attached to it. The risk unfortunately exceeded the benefit in that situation.

In my own personal practice of some cumulative, about 3,000 people on troglitazone, I've had five liver function test abnormalities. These are biochemical abnormalities, mild rises in ALT to less than 100. The agent was discontinued. All five improved and got better and had no permanent sequelae.

It is my contention that in a risk-benefit analysis in this vascular scourge of diabetes looking at the overall nexus of action of this very exciting compound, troglitazone, that this is the forerunner in order to cut down on the death by cardiovascular disease.

If one looks at a risk-benefit analysis, the benefits so far outweigh the risks that I hope and my charge to the Committee is that hopefully science will prevail and not emotion.

And I thank you very much for your attention.

CHAIRMAN BONE: Thank you very much for your remarks, Dr. Miller.

The next speaker is Dr. Robert Busch from Endocrinology Group in Albany, New York.

DR. BUSCH: Thank you for the privilege to be able to present to you today.

I'm a clinical associate Professor of Medicine at Albany Medical College, but I'm a practicing endocrinologist in a group of ten private practice endocrinologists in Albany, New York, and I'm here today representing myself, my ten partners who are endocrinologists, and our 2,000 patients who are on troglitazone therapy.

In practice, we have the luxury of working with a Doctor of Pharmacy from Albany Medical College, and Dr. Michael Kane has tracked our patients, two of the providers who started patients on troglitazone in 1997. He is submitting this for publication and for presentation at the American Diabetes Association in

June.

We had 460 patients who are on our best effort therapy with either insulin, sulfonylurea, or metformin therapy, with a body mass index on the average of 31. These patients were started on troglitazone in 1997, and over 95 percent of the patients are still on troglitazone therapy.

Five patients had to be discontinued because of ALT elevation between three and eight times normal, which reversed to normal. That's 1.2 percent of the patients the drug had to be stopped because of transient ALT elevation.

Of the 95 percent of patients still on troglitazone, the average hemoglobin A1c in these patients with our best effort as endocrinologists was 8.2 in 1997, a B minus or C plus. Now, our average A1c is 7.3, a decrease of .9 sustained over the past year.

This is reminiscent of the U.K. PDS decrease in hemoglobin A1c of .9, which significantly decreased the microvascular complications of diabetes.

I did not bring slides today, but I did bring two of my patients from Albany, Ms. Lucille Lorenzo, who is a woman who has had diabetes for 20 years, on insulin previously. She's a mother of six,

grandmother of 12. Her A1c was 8.9, today is in the mid-six range on troglitazone with sulfonylurea and metformin.

A second patient, Robert Anderson, who's a leasing manager for the state. Also, his avocation is as a farmer, and when he was on multiple injections of insulin he had significant hypoglycemic reactions when he was milking his cows. Now on troglitazone, repeglonide and metformin therapy, he can mow hay with his grandson.

Now, these are just two of the patients that we have as a practice, that we could fill this room with patients who have benefitted from troglitazone. Unfortunately in our area, a lot of the primary care physicians are influenced by what's in the media, and they're practicing medicine by media, and their patients have not been exposed to troglitazone because of fear of the media.

Now, the public opinion is influenced by whom the public hears, and oftentimes the public only hears silence, and my hope and the faith that I have and my patients have in this advisory panel and in the FDA is you be very loud and very vocal in your reaffirmation of the safety and efficacy of troglitazone in benefitting the lives of our patients

with diabetes.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Busch.

The next speaker is Dr. Edelman from the Veterans' Affairs Hospital in San Diego, California.

DR. EDELMAN: Thank you for allowing me to testify before you today on this very important issue.

I'd first like to tell you that I am on the Speakers Bureau for Parke-Davis, Bristol-Myers Squibb, Bayer, Lilly, and many other diabetes related companies. However, I am here today for my patients, and I have come on my own time and my own money.

I am not only a physician who specializes in taking care of people with diabetes, but I have also been living with diabetes for the past 28 years. Although my type of diabetes is quite different from those who could benefit from Rezulin therapy, we share some of the same day-to-day trials and tribulations of balancing our diet, exercise, and medications in order to maintain good glucose control, and it is not an easy task, and the more tools we have to overcome the many barriers to good glucose control, the easier it becomes.

We know the consequences of poorly

controlled diabetes: blindness, dialysis, amputations, heart attacks, strokes, depression, and unfortunately much, much more. Every day in America over 400 people die directly due to the effects of diabetes, and it's so important to look at the risk of Rezulin versus the benefits of improved glucose control when you're looking at a very serious disorder that affects the quality of life of millions of Americans on a day-to-day basis.

If one death is too many, then, yes, take Rezulin off the market, but then you must also take off glucofos insulin, sulfonylureas, Motrin, aspirin, Tylenol, and many other medications used to treat patients with cancer and HIV.

I follow over 500 people at the Veterans' Affairs Medical Center in UCSD who are taking Rezulin therapy. You can't buy this drug back from these individuals because it has helped them to achieve and maintain control over their diabetes where previously it was not possible despite intensive efforts.

This is why two of my patients, James Roach and Ray Cordova are here with me today. These gentlemen and many other of my patients would be at a serious disadvantage if they were not able to continue therapy with Rezulin in order to achieve good glycemic

control over the long term.

I challenge anybody in this room to find a physician who has used Rezulin in more than just a handful of patients and did not find it a very impressive drug not only as in monotherapy, but also as in combination therapy with other drugs and with insulin, especially to achieve the clearly defined goals put forth by the American Diabetes Association.

In my observation, the only nay sayers are the individuals with little or no practical experience with Rezulin, and they have not spoken to the 1.5 million people with diabetes who have benefitted from the use of this drug.

Now, no drug is 100 percent safe. However, diabetes is a serious disease whose prevalence is increasing quite dramatically not only in the United States, but also around the world. Every drug has a risk-benefit ratio, and in the case of Rezulin, the benefits of reducing eye, kidney, nerve, and heart disease far outweigh the risk of liver disease, especially with proper liver function monitoring.

Every day 1,600 people in the United States are diagnosed with diabetes, and in any 24-hour period 400 people die directly due to the

complications of diabetes. I think we have to continue to be as aggressive as possible to reduce the huge amount of suffering that's associated with this disease.

Thank you very much.

CHAIRMAN BONE: Thank you, Dr. Edelman.

Our next speaker is Dr. Boyle, Dr. Patrick Boyle from the University of New Mexico Health Sciences Center.

PARTICIPANT: It doesn't look like he's here.

CHAIRMAN BONE: All right. If Dr. Boyle appears later, if he'll make himself known.

We'll move on to Dr. Anne Peters, Director for Clinical Diabetes Program at the University of California, Los Angeles.

DR. PETERS: Good morning. I'm Dr. Anne Peters, and if I can have the first slide.

I'd first like to disclose that I have received funding for research, speaking, and consulting from the following pharmaceutical companies. I do not own stock in any pharmaceutical company, and no one sponsored me to come here today.

This equation is central to medical decision making. Recently we've all learned that the

risks of a drug can be sensationalized, but psychologists know this. We all remember traumas far more than we remember the good things that happen to us. It is the bad things that we tend to recall.

So I'm here today to discuss the benefits of Rezulin and the benefits of treating diabetes, but this does not mean I do not understand the harms.

The woman on the right is my great aunt Helen. She died last year of a drug reaction to naprosin. Does this mean that I don't use drugs? No, but it means that I use drugs with an appreciation for maximizing the benefits and minimizing the risks.

But what of Rezulin? Let my patients tell you. This is Delores. Because of Rezulin, she was able to stop insulin.

This is Sheila. On a combination of Rezulin and glucophage, she was able to cut her insulin dose in half and is now able to lose weight.

This is Sylvano, who was never even able to come close to a normal hemoglobin A1c level until Rezulin was added.

This is Steffie. Steffie had such bad pain in her feet and legs from her peripheral diabetic neuropathy that she could barely walk in from her car in the parking lot to clinic. When Rezulin was added,

her hemoglobin A1c level came down to normal. Her pain is gone. Just a few weeks ago, she was able to turn in her handicapped parking placard and now can walk through the parking lot to clinic without pain.

And finally, this is the rabbi who says, "What would I do without my Rezulin?"

(Laughter.)

DR. PETERS: Now, these are but a few of the hundreds of patients I have successfully treated with Rezulin, but what of the risk of diabetes? Diabetes is a deadly disease. This slide depicts the 17 people who will die this hour because of the complications of diabetes.

And this, this is Pat. Just last week Pat went permanently blind from her diabetic retinopathy. Pat and I are exactly the same age. Yet Pat is gravely disabled. She asked me to ask the FDA to hurry and approve new drugs that can help people with diabetes so they don't have to have the terrible complications she has suffered.

And finally, back to the original equation. I do not believe that an individual physician can determine the risks of a drug therapy. That is for the advisory panel and the FDA to do.

But I ask you that you do this without

bias, that you do this without the bias of emotion, that you do it without the bias of the media, politicians, the pharmaceutical industry, anyone. These decisions must be made based on the most rational, scientific evidence we have available.

On the benefit side, in my hands Rezulin has been a very safe and effective drug. I urge you to keep it on the market if, on a population level, this equation continues to be strongly positive.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Peters.

The next presentation will be by Dr. Cooppan, the Jocelyn Diabetes Center in Boston.

DR. COOPPAN: Thank you very much, Mr. Chairman.

My name is Ramachandiran Cooppan, and I'm a senior physician at the Jocelyn Diabetes Center in Boston, where I've been on staff since 1975. I've come on my own volition, and I'm not representing the institution, but as a physician who has spent the last 24 years treating patients with diabetes.

I'm also on the Speaker Bureau of Parke-Davis, Bristol-Myers Squibb, NovoNordisk, Eli Lilly.

In 1998, the Jocelyn Diabetes Center

celebrated its 100th anniversary, an institution that was dedicated itself to the welfare and care of patients with diabetes.

In the last 25 years, we have seen a great increase in our understanding of the pathophysiology of Type 2 diabetes, and one thing is clinically evident to all of us. We start our treatments far too late with this disease. At the time of diagnosis, our patients already have complications.

We have been hampered in the past by not having available multiple strategies and therapies to intervene in this disease. Furthermore, we're in an era now where we have outcomes data. The U.K. PDS, United Kingdom Prospective Diabetes Study, and the DCCT give us the information that we need to make the case that diabetes control matters.

When I first arrived at the Jocelyn Diabetes Center in 1974, we only had the sulfonylureas and animal source insulin. We've advanced our insulin therapy remarkably. We now have the challenge to open ourselves up to new medications in the oral arena.

The advent of metformin in 1993, which the FDA approved in its wisdom, opened combination treatment to us once again, but this was an old treatment first reported in 1953 by Sam Biezer.

The advent of troglitazone opened a new era for us. Not only did it open a window into our understanding of the pathophysiology of diabetes, but it addressed a fundamental defect in the disease, that of insulin resistance.

The U.K. PDS has taught us that no monotherapy is going to succeed in diabetes management. The case has to be made for combination treatment.

In a preliminary analysis of over 2,000 patients taken care of at Jocelyn Diabetes Center, we have had no case of liver failure of jaundice. We have had less than ten patients who have had elevation of their liver function studies, all of which return to normal with cessation of the drug.

This in no small way was due to the exercising of a great degree of pharmaco-vigilance on our part. We monitored the patients. We adhered to the guidelines. We find that the insulin sensitized troglitazone is a very useful tool in our armamentarium, and we believe sincerely that the future of diabetes management belongs to combination treatment and that, indeed, we will actually see new treatments emerging in the future and combinations of two or three drugs will be necessary.

In conclusion, diabetes has been described as a moving target. We need to have therapies that are evolving with this disease. This disease will not only test the science of medicine. It will also test our art of the practice of medicine.

Thank you very much, Mr. Chairman.

CHAIRMAN BONE: Than you very much, Dr. Cooppan.

The next speaker is Tom Halstead, listed as President of Hemotherapy.

MR. HALSTEAD: Thank you, Henry.

I have no relationship to any drug company.

Ladies and gentlemen, distinguished physicians, dearest patients, of the over 3,600 FDA approved drugs on the market, more than 1,100 can potentially damage the liver. Despite its great benefits to diabetic patients, Rezulin is a member of this latter category and the subject of today's discussion.

Could there be a way to reap the benefits of Rezulin yet obviate its negative effects on the liver? We believe so.

Hemotherapies offers the only liver assist device available worldwide. Called the Biologic DT,

it has been cleared by the FDA for use in treating patients with liver failure and patients with drug overdose, including those drugs that result in liver failure.

A single treatment by our device can restore the normal liver function to patients with liver failure due to drug effects. We believe that this detoxification device could dramatically bolster the safety profile of Rezulin and many other drugs.

The Biologic DT was designed to provide temporary support of patients with acute liver failure. Unlike renal dialysis, the Biologic DT process is much gentler. The device is much simpler to operate, and lifelong treatments are unnecessary.

Using a unique sorbin suspension, the Biologic DT acts as a second liver, immediately clearly drug metabolites and numerous liver toxins from a patient's system. The build-up of these toxins can lead to encephalopathy, coma, and even death.

We have seen the benefits of the Biologic DT even for patients in coma due to liver failure. There have been patients listed as "do not resuscitate" and patients needing liver transplants whose livers have been brought back to normal function by the Biologic DT liver detoxification process,

following serious drug overdose or liver failure from other causes.

Some researchers are even using the device with previously dangerous doses of oncolytics with dramatic positive effects against cancer.

The Biologic DT device has only recently been available beyond trial centers in the U.S. The Rezulin researchers community, physicians, and patients were not aware of this treatment option for patients developing liver problems after the use of Rezulin.

Although we have no relationship with the manufacturer of the drug, we are confident that when careful liver function monitoring indicates a patient is progressing to liver failure after the use of Rezulin, our technology should enable a physician to treat such patients and assure that they recover normal liver function. The benefits of Rezulin could then be provided with much greater safety, confirming the wisdom of the initial drug approval.

We are eager to work with physicians to prove the ability of this new technology to reverse liver failure in the rare patient developing this complication after the use of Rezulin.

Friends, Rezulin is only one of over 1,100

drugs on the market today that can potentially damage the liver. In fact, one only needs to look in the family medicine cabinet to find a number of drugs which could result in severe liver failure. For example, when abused, acetaminophen has the potential to cause serious liver harm, especially when mixed with alcohol, a cautionary note to any young drinkers who think that taking an acetaminophen before going out drinking can avoid a hangover. This is patently false.

Further information on the Hemotherapy's Biological DT device and the technology behind it is available. We thank the FDA for giving us the opportunity to raise this option, and our best wishes to all of the patients and their families.

CHAIRMAN BONE: Thank you.

The next speaker is Dr. Khan from Hennepin County Medical Center and the University of Minnesota Diabetes Unit, and I understand that Dr. Boyle is here. So we'll work him in in a little while.

DR. KHAN: Thank you.

Mr. Chairman, ladies and gentlemen, I thank you for the opportunity to speak for a few minutes in front of you. I am on the Speakers Bureau for a number of pharmaceutical companies and have

served as a consultant and advisor to a number, including Merck, Pfizer, and Parke-Davis, amongst others.

I'm here voluntarily and on my own time and expense and to express my views and experience, again, with patients with diabetes in Minneapolis.

As head of the Department of Endocrinology at Hennepin, where we have some 4,000 patients coming through our program with diabetes, the vast majority of those are patients with Type 2 diabetes. And like many inner city hospitals in this country, a significant majority of those are people of color or indigent patients from the inner city population. This population is a population which is considered high risk for many co-morbid conditions, including diseases of the liver from many causes, including alcohol, including drug abuse, et cetera.

And in that patient population with effective screening and effective monitoring, we have treated several hundred patients with Rezulin, and to date have had five patients with an elevated enzyme, and most of those, except for one, has recovered. The other one has only recently been found to have an elevated enzyme, and we anticipate over time that will also normalize.

My point that I'd like to express today is that death or loss of an organ for any cause is a disaster both for the patient and for the family. Patients and their physicians don't choose that, but just like that, patients and their physicians don't choose diabetes. Of all the thousands of patients that we have in Minneapolis coming to our program with diabetes, none of them chose to get diabetes.

And when we choose to pick a drug or drugs for them, we do that because we have no alternative. Most of these patients, as has been shown in academic trials have been through other therapies by the time they come to an endocrinology practice and are referred for alternatives as to what are my options, Doctor.

And when we look at those options, we have to balance what is safe for the patient and, on the other side, look at it and say, "If I don't treat this patient, what's going to happen?"

Well, we all know that diabetes is the number one cause of blindness in this country. It is also the major and probably will soon become the number one cause of kidney failure in this country also, as well as the fact of the number one cause of leg amputation and a major cause of strokes, et

cetera. Patients don't want that either, and as we treat them, what we're actually saying to them is that without treatment this is the outcome, and with treatment here are the possible risks.

And members of this Committee know as well as I, in many cases better than I, that we have to balance those two risks. My battle with patients with diabetes -- and maybe "battle" is not the appropriate word -- but the challenge that I have is trying to get them motivated and maintained on their treatment.

Ask any physician how difficult it is to maintain a patient with a chronic disease. That job is not made easier when we have sensationalized media that presents opinions without scientific fact or in a balanced manner.

What that means is that not only does a very difficult job in the clinical setting become ever harder, but we lose patients to effective therapies, and my request to you as a Committee is to look at the science and the balance of the community's experience with all the products, and the reality is that the U.K. PDS has shown we do not have evidence that one drug can maintain diabetes control. Perhaps in the long term combinations of therapies can.

And finally, we are not just treating

blood sugar. I think this is getting increasingly discussed in the literature. We know that diabetes has multiple facets, beta cell dysfunction, insulin resistance, and we in the past have been reasonably successful in the short term affecting beta cell dysfunction. We've not had the ability to treat peripheral resistance, which probably is the major cause of cardiovascular death, alongside the dyslipidemia, hypertension, and diabetes.

And so to conclude, I would like to request that we take this in a balance view. Patients do not choose to have diabetes. We do not choose for them to have complications.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Khan.

Next we have Dr. Moore from George Washington University, Center for Health Policy Research, and we'll have Dr. Boyle after that, to be followed by Dr. Bautista.

MR. MOORE: Good morning. My name is Thomas Moore. I'm a Fellow in Health Policy at George Washington University.

The views I'm expressing here are entirely my own and do not reflect any institution with which I'm affiliated or providing advice as a consultant.

I am the author of a book called Deadly Medicine. It is a case study of the worst drug disaster we had in our nation's history in which thousands of heart patients died of cardiac arrest because of antiarrhythmic drugs whose hazards were not fully appreciate.

While the risks and benefits of Rezulin are of quite a different order, there are some surprising similarities to the discussion that is being held today and the discussion that was held before some of the antiarrhythmic agents were first marketed.

An issue is not so much the risks, but how we think about benefits. In this spectrum here, it seems to me the top items are well known to everybody in this room, and that, of course, the drugs that are at the top of the benefit ladder are among the most important scientific discoveries in the history of medicine.

Let me go straight to the part where my views might seem more controversial. Drugs that prevent harm, and I would include in this group the cholesterol lowering drugs and the hypertension drugs, I place very much down the ladder of benefits towards the bottom, and why do I say so? Isn't it important

to prevent heart attacks and strokes? And certainly these drugs have that demonstrated capacity.

The answer is that the benefit rate is very low. On an annualized basis, the treatment of mild hypertension benefits about four per 1,000 treated per year. The best cholesterol data looks a little better than that, about six per 1,000 per year in terms of clinical benefit, meaning a heart attack prevented, a stroke prevented or something of that order.

Why is that important to think about in discussing Rezulin? Because if you are only helping about one-half of one percent per year in terms of a tangible clinical benefit, in terms of making them healthier, then you have to be very sensitive to the risks to which you expose those patients.

At the very bottom of that, below drugs that prevent harm are drugs that we don't know for sure because they haven't been out there long enough and tested for enough years, actually provide the clinical benefit, and we hope through using a surrogate endpoint that they do.

But we've had a lot of experience with surrogate endpoints, and we know we're not always right when we make this gamble. We have had class

after class of drugs where the experts are as deeply committed to their patients as are the specialists in this room, believed that positive antitropes, antiarrhythmic drugs, fibric acid derivatives, nesoldipine and Type 2 diabetes. In all of these cases there were compelling reasons to believe that there was a benefit. When the long-term studies were done, excess mortality was seen.

So where does the surrogate endpoint -- and when we are talking about the benefit of Rezulin today, we're saying what surrogate endpoint does it have an effect on. How does HbA1c stand?

It strikes me that scientifically it is actually quite superior to blood pressure and cholesterol lowering as a surrogate marker because it is involved with fewer and less complex body processes. So on scientific terms, it strikes me as a strikingly valuable surrogate endpoint.

But when we look at the actual clinical effects of this drug as we have seen and actually tested in clinical trials, the results were extremely limited.

You can see all of the items here which everyone has referred to, the U.K. PDS trial earlier. The overall risk reduction with the sulfonylureas was

a mere 12 percent from a combined endpoint that mainly included reduced incidence of photocoagulation treatments.

When we look at the real hard endpoints for diabetes related disorders, we do not see an effect.

We have metformin, which was very problematical, and in fact, in combination therapy the drug seemed to have excess mortality, a warning flag that should trouble us all.

And in addition, we know the benefits are very, very small here because it took ten years and hundreds of patients to even register a small effect on a combined endpoint.

So when we make decisions about the risks and benefits with drugs, we have to realize that what we're doing is this -- oops, not that way.

(Laughter.)

DR. MOORE: We're gambling. We are gambling with people's lives, and if you are going to make this gamble, it seems to me that you need to have a drug that, number one, has a dramatic effect on the surrogate endpoint in question and, number two, that has extremely low risk.

Yes.

Now, where in the spectrum of moving a surrogate endpoint does it appear that Rezulin resides? And here I think we ought to start the simplest way to look at a drug is its monotherapy trial.

The Committee did not see this. This is from the supplemental indication for monotherapy, and these patients were placed on this drug, and the trial commenced.

Now, the important thing to remember is of those 314 patients, a very large number of them had been on a previous therapy, and so these were the benefits that were seen. In fact, as you can see from the medical review, they never actually achieved the level of glycemic control that they had in preceding therapy. They actually increased from baseline.

Now, I have some questions about the ringing endorsements of a drug which when given to patients as monotherapy, they got worse.

Now, fortunately, I suppose, for Rezulin there was another small group of patients in this monotherapy trial who had not been on -- previously treated on drugs and in fact were on diet therapy alone. The results were no better, and in fact, in only one group of 15 patients was a benefit found in

HbA1c, a reduction of a little over one percent.

Now, the medical review, I think, says rather eloquently the performance of this drug in monotherapy is extremely weak, and in fact, I find this to be among the weakest evidence in support of an indication of a drug in many, many years of looking at drugs.

The issue really I see in looking through all of the indications is responders, and the problem that I see in this drug is the low response rate. As you can see, I've picked all three indications, and in most cases, the response rate of the patients is really quite low, best with glyburide here. That's 400 milligrams. For the three bar that's the 400 milligram dose, but the fact is in terms of achieving a significant change in this surrogate marker, which we hope will predict a health benefit ten years from now, this is not changing the surrogate marker in a large number of patients.

I'm equally concerned when we look at the patients in whom it does achieve a significant clinical effect. As you see, when patients do respond, we see a significant weight gain, and I think more analysis -- and I would urge the Committee to ask for a separate analysis from the company of whether or

not responders consistently across a whole spectrum have weight gain because if you have a small benefit in terms of reduced complication of diabetes and an increased risk because of obesity, it is once again not clear whether you've done more good than harm.

Finally, let's just look at this drug at its best. Here is a group of patients where you really do have a significant change in your surrogate marker, minus 1.29, in combination with insulin. What adverse effects were observed in that very same population?

I've subtracted this from the placebo, but in hopes of making a change in a surrogate marker which might help over many years, we see a lot of individuals have suffered actual harm from the treatment.

My view is this drug simply is not worth the risk. It has too many problems. There are safer alternatives, and more effective drugs available, and I agree with the British who have found that the benefits of this drug simply do not outweigh its risks.

Thank you.

CHAIRMAN BONE: The next speaker will be Dr. Boyle. I understand that Dr. Boyle is here now.

Thank you.

DR. BOYLE: Thank you.

It's an honor to have the opportunity to talk to you this morning and perhaps speak on behalf of people with diabetes from a couple of different levels.

I'm a member of the American Diabetes Association, National Board of Directors, and serve as the Diabetes Care Management Coordinator for 3,500 patients with Type 2 diabetes at the University of New Mexico.

These are the bottom line results from the United Kingdom Prospective Diabetes Study, which has been alluded to several times here this morning, and just dropping the hemoglobin A1c from an average of about 7.9 down to 7.0 reduced any endpoint associated with diabetes. That's blindness, heart disease, amputations, kidney failure by 12 percent.

It reduced microcirculatory disease by 24 percent, and there was a trend, although not statistically significant, from macrovascular complications to drop by 16 percent, but the p value was .052, but all of this is going in the right direction to suggest that small decrements in glucose concentration lead to enormous changes in the risks

associated with this disease in the long run.

Yet one of the sad parts of this trial was that in the initial one to two years shown on the X axis there was a nice decrement in this marker of good glucose control, hemoglobin A1c, that was not then subsequently sustained in the years from two out to ten years on monotherapy, and unfortunately in the United States, this is a particular problem, that people stick with one drug rather than thinking of this as an issue that requires multiple different interventions, and it's led to in the United States a hemoglobin A1c on average of nine and a half percent, which is well above the control group used in the USPDS with diet and exercise alone.

So it is absolutely no wonder to us in the American Diabetes Association and those providing care to people with diabetes in this country that we are spending $140 billion a year taking care of this disease process. That's four percent of the gross national product of the United States to one single disease.

Let me tell you about the population that I serve. The 3,500 patients at the University of New Mexico who have Type 2 diabetes are, in large part, people of color. They are over 50 percent Hispanic,

and then we have about a 15 percent Native American population that comprise our population, and half of them are medically indigent.

Over $18 million a year are spent on managing their endstage complications. They are 14.9 percent of the total population of our university hospital. This is a growing problem. It is not six percent of the U.S. population. It is increasingly becoming a disease that is not affecting people in their 50s and 60s, but instead affecting 20 year olds and now people in their teens in my state.

Let me tell you that in 1994, the conclusion of the diabetes control and complication trials for which we were members, we went out and looked in the general medicine clinic and found that the mean glycosylated hemoglobin in our patient population was 5.6 percentage points above the upper limit of normal. I'm not proud to say that, but one-third of the patients were within one percentage of the upper limit of normal.

By October and November of 1977, with the advent of metformin in the United States and subsequently earlier in 1997 the addition of troglitazone to our armamentarium, you now seen in green that we've taken the same patient population and

have over 50 percent of them at target by using aggressive combinations of all of the available tools, and in this case about 14 percent of the patients overall are taking troglitazone because they failed on metformin plus sulfonylurea.

In January of this year, taking 160 of those charts, randomly selected out of the 3,500 patients, we now have 66 percent of our patients to within the American Diabetes Association goal at less than seven percent.

If you look at the toxicities associated with each one of these medications, you can see that all the common things that we use right now carry with them morbidity and mortality, and in fact, if you look at sulfonylureas on the far left-hand side, it's about one in 30,000 mortality rate as noted in the Clinical Endocrinology and Metabolism Journal.

In the middle, in the first million patients put on metformin in the United States, from the FDA's own data in a letter to the New England Journal, you can see that approximately one in 50,000 people in the country in the first million patients put on this medication, which was a major adjunct to our therapy, one in 50,000 ended up suffering a fatal event.

Finally, with troglitazone in the first 1.5 million patients put on this medication there is about an incidence of one in 60,000 fatal events.

What's killing these patients? If you look at 1980, going forward to 1996, you can see this information from the U.S. Center for Health Sciences adapted from a summary from recommendations from a congressionally mandated committee called Diabetes Research Work Groups, that since 1980 there's been a rough 20 percent, 25 percent fall and stroke and cardiovascular disease. Cancer has stayed roughly steady, while diabetes has increased as a cause of death in the United States by 20 to 30 percent over the same time frame.

So I would ask you as members of this Committee not to be blind to diabetes. This is a major public health care problem for which we need every tool that we can possibly have at this point. The relative risks of using this medication are no different than any other, and I would say, based on our evidence from 3,500 patients, which is a small microcosm of society, that this has been a major additional tool for our treatment of patients with Type 2 diabetes.

Thank you.

CHAIRMAN BONE: Next will be Dr. Jose Louis Bautista from Fresno, California.

DR. BAUTISTA: I'm Dr. Bautista from Fresno, and I thank you for allowing me to speak.

I'm here to -- I'm also a speaker, and I also do research for multiple drug companies. I'm here to ask you not to remove Rezulin from the market for the following reasons.

I'm in charge of over 30,000 lives in my practice. Almost ten percent of those have diabetes, which is close to 3,000. I stopped at about 400, the number of patients that I have on Rezulin, and two of them have developed complications.

One is a lady that was on Rezulin, developed Hepatitis A. I stopped the Rezulin. The patient is doing fine now, Rezulin.

The other one was a young man who became an alcoholic after he had family problems, on Rezulin, and I stopped the Rezulin. He's doing fine. He's still fighting his problems with his wife.

But what I have seen in the last years is that the Type 2 diabetes patient is not created equal. He presents or she presents with different stages, and I've been able to develop on my own protocol in my group, based on fasting C peptide and fasting insulin,

the first stage I have labeled it a normal secreter which has C peptide of 3.0 to 4.0 with a normal insulin, but had a normal hemoglobin A1c and a normal glucose.

This patient, they failed diet, exercise and weight loss. I put them on an insulin sensitizer like Rezulin, and they do really well, but when I put them on a sulfonylurea, they become hypoglycemic.

The second stage is a group that becomes -- that I label hypersecreter, has a C peptide of greater than four, elevated fasting C peptide, elevated hemoglobin A1c, and also an elevated fasting sugar. These patients do extremely well with Rezulin, but they do lousy when you put them on the sulfonylurea. They become hypoglycemic.

The third stage, I have labeled them as a hyposecreter. They have a C peptide of 2.0, but less than 3.0, has a fasting insulin level less than ten, has elevated hemoglobin A1c, and also a terrible fasting blood sugar. These patients do really well with sulfonylureas, but they do much better when you do a combination treatment with a sulfonylurea and an insulin sensitizer like Rezulin.

And the final stage is a group that I label the microsecreter, have a fasting C peptide less

than 1.9, a fasting insulin level of less than, God, five, and also have an extremely elevated hemoglobin A1c and also elevated fasting blood sugars. These patients do well with insulin, but they do much better when you do a combination treatment of insulin with Rezulin, an insulin sensitizer.

So in summary, I don't have a perfect protocol, but it's working for me. But what I have seen is that a Type 2 diabetic patient presents in different stages, and we need to be careful with insulin resistance.

All I know is that in my group I see a lot of insulin resistance. It seems like in all the four stages we see insulin resistance, and we need a good insulin sensitizer. I think Rezulin pound by pound is the strongest we have, and therefore, I strongly recommend that you don't remove it from the market.

Thank you.

CHAIRMAN BONE: Thank you very much, Dr. Bautista.

The next speaker is Dr. Einhorn, who is from the University of California, San Diego.

DR. EINHORN: Thank you.

CHAIRMAN BONE: And from Sharp HealthCare, I guess, right?

DR. EINHORN: Yeah, a few too many words there, I noticed.

Thank you for the opportunity to participate. It's humbling to follow such articulate colleagues. I've had to rewrite my talk every four minutes to try to not repeat, but let's see if we can offer something to the group.

I'm Daniel Einhorn, and I've been practicing in San Diego since 1984 with my partners, Eric Gold and Ray Fink, and we felt we have to support this process of trying to look objectively at clinical data in a peer reviewed way rather than any other forum. I'm not sure we realized how popular this meeting would be, but we wanted to help.

And my remarks are based on our experience with about 1,500 patients using troglitazone by and large with other agents, and this experience will be presented at the annual meeting of the American Association of Clinical Endocrinologists. So I want to make a few disclaimers.

First, I've come as a private citizen, paying my own way, representing my partners and my patients, but like most of the endocrinologists in this room, we do work with whoever can help us participate in clinical research, Speakers Bureaus,

including those for Parke-Davis.

But we really have no vested interest in the outcome of this meeting other than we really need to help resolve the ambiguities about troglitazone because we need to know what to teach and how to practice.

We typically see more seriously affected individuals with Type 2 or they wouldn't come to us. So by and large, since there's no one wonder drug, we're using agents in combination.

There's no question in our experience that troglitazone has enhanced metabolic control, as you've heard from the others. Of 1,500 cases, and we did very careful liver and, frankly, kidney monitoring from the outset as we do with any new drug, certainly a new class of drugs, and out of our 1,500, we had to withdraw five from Rezulin. There were three others where clearly it was other issues that had nothing to do with the drug, but certainly that's a safety profile that seems comparable with anything else that we have used, if not better.

I'm not sure why our numbers look a little better than the numbers looked in the studies. We actually do have patients that maybe take better care of themselves, perhaps less alcoholism and that sort

of things, but still it's been a very safe drug.

Our conclusions really are that we have been part of a kinder and gentler approach to managing our patients with diabetes. I think the issues of improved metabolic control are clear: improvement in lifestyle. The ability to, as you heard from some of the other speakers, to come to meetings, to do the jobs you want to do, to be with your family the way you want to be is extraordinary with combination therapy as compared to how things were before.

Do we worry when we prescribe Rezulin? Absolutely. We worry when we prescribe anything, and see that as our job, as clinical endocrinologists, to frankly worry about our patients and to do the monitoring carefully, and I think that's not going to change, and that's not going to change with any class of drugs.

And, frankly, if this hearing today does show us strong evidence that we're dealing with something less safe than others, we'll turn on the dime, but in our experience Rezulin has clearly been safe and effective, has had no more of the risk profile than other agents we've used, and has clearly improved the lives of our patients with Type 2 diabetes.

Thank you.

CHAIRMAN BONE: Thank you very much.

The next speaker is Dr. William Clark from Houston, Texas.

DR. CLARK: Thank you.

I'm here for my patients. I'm also on the Speakers Bureau of several drug companies, but I spent my own money to come here today.

I've had experience treating diabetics for 13 years. I care about the quality of their lives.

For the first ten years, my experience was that they slowly deteriorated. Then with the development of Rezulin, I felt that had a chance to slow that down or maybe even improve the qualities of some of their lives, and I have over 500 patients on Rezulin. I've not had any elevated liver enzymes in any of these.

I'd like to tell you about a couple of my patients. One is now in his late 60s. He's published a community newspaper there in Houston for over 30 years. He's been insulin dependent for eight years. Four years ago he lost the sight in his right eye, and two years ago his left eye began to fail, and he started trying to sell his newspaper.

We got him started on Rezulin. The vision

in that left eye stabilized. In Texas, they have, I guess, a place where the newspapers submit their best work every year to see who wins the most awards. Last month he won the most awards of any newspaper in Texas and the most awards that he's ever won.

I have another patient that I think Rezulin has made a big difference in. This is a patient who's in his mid-50s, had a large counseling practice in Houston. Two years ago his younger sister died from complications of diabetes. A few years before that his mother died from diabetes after having both of her legs amputated.

James had sort of a borderline abnormal GTT, had a post prandial insulin that was usually between 30 and 60, but he felt bad. The oral agents, the sulfonylureas made him feel worse. He gave up his radio talk show. He didn't feel like running a big practice. He decreased the number of his clients, let his health go, and a year ago started on Rezulin.

Since then, I think after two weeks he said he felt the best he's felt in years. He's now hired back some of his counselors. He's negotiating to start his radio talk show again.

And I don't know. I've seen in the 500 patients a lot of examples like this. I feel asking

people to treat diabetes now without Rezulin would be like asking a coach to win a track meet after cutting off a leg of all of his athletes.

I think if you notice here today none of the people that are treating diabetes have advocated pulling this drug off the market.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Clark.

The next speaker is Dr. Vincent Pearson from Johns Hopkins Hospital.

DR. PEARSON: Thank you, Mr. Chairman.

Good morning, ladies and gentlemen. I come to you as a pharmacist, as a clinical coordinator of drug information at the Johns Hopkins Hospital in Baltimore.

I have received research support from both Bristol-Myers Squibb and Pfizer, but the views I'm going to express are purely my own based upon my experience.

My charge as a drug information pharmacist is to review information about drugs and drug products as they are released in the market, and especially when they come before our hospital's Pharmacy and Therapeutics Committee for review and consideration to be included onto our formulary.

When troglitazone was first introduced over a year ago, I was very impressed with the published data that was surrounding the product. However, we were all acutely aware of the liver toxicity that was associated with the product. Therefore, the committee, in its wisdom, opted to table a decision on the drug.

We still have yet to bring this to closure. Why? Because myself and several other people on our faculty have tried as best we could to get our arms around the scope and the depth of the liver toxicity issue, unfortunately to no success.

In our minds, there are several key issues that I would like to leave before this Committee this morning.

First, we must get a true handle on the numbers of deaths that have been at least associated with the drug and get as strong a collection of that number as it can be.

Second, we must take that number and from that ask ourselves which of those deaths are truly due to the drug's playing a significant role, my personal definition of the word "significant" being a large enough and broad enough role such that in the absence of any other confounding factors this drug can truly

be said to be at least a causative factor.

Once you've taken that number, the next charge is to put that number over a denominator that consists of the number of patients who have received the drug and have done well on the product.

I'll admit my bias is towards the in-patient population. So most of my experience comes from those patients who have had adverse reactions due to the drug. My charge is to monitor the adverse drug reaction monitoring system as mandated by the Joint Commission of Accreditation of Hospital Organizations in our hospital.

Lastly, I would ask that once you have looked at that numerator of deaths that are truly significantly due to the drug versus the denominator of people who have gotten the drug and have done well, we must ask ourselves: are we comfortable with this ratio?

If we are comfortable with this ratio, then the drug deserves to remain on the market. However, if we are not comfortable with this ration and can truly feel that we can do better with drugs that are either currently available or are coming through the pipeline, then the drug deserves serious consideration from being pulled from the market.

I will leave as my parting shot one last thing that we haven't talked about this morning. As a practicing pharmacist, we are charged with filling medication orders for many different prescribers. One of our common problems is not having the correct information to field questions from prescribers regarding the status of drug products.

Therefore, I would ask that when we finally reach a decision regarding this drug, that the information upon which that decision was based is made readily available to most practicing pharmacists. Thus, if a pharmacist gets the question from a prescriber what became of troglitazone, the pharmacist can confidently go back and say, "This is what happened to true troglitazone, and this is the reason why it happened."

Thank all of you for your attention.

CHAIRMAN BONE: Thank you very much.

This concludes the regular open public hearing section.

We have now remarks by Dr. Sidney Wolfe, Director of the Public Citizens Health Research Group.

DR. WOLFE: Thank you.

The last time I appeared before this Advisory Committee concerning a diabetes drug was 22

years ago. The drug was phenformin, also said to have a unique mechanism of action and whose withdrawal from the market was strongly opposed by many diabetes experts. Like troglitazone, it also had a unique type of toxicity, lactic acidosis, fatal in about 50 percent of those patients who developed the abnormality.

After a lawsuit against the FDA by our organization, it was banned as an imminent hazard to the public health in 1977. By then hundreds of patients had died as a result of this drug.

I'm going to talk first about some case reports concerning this drug and then some incidence discussion of the problems.

John Doe was an otherwise healthy 45 year old Washington, D.C. policeman started on Rezulin in the late summer of 1998, preceded by perfectly normal liver texts. Within a week after starting the drug, well before he was due for another liver test, he became seriously ill, was hospitalized at Johns Hopkins with acute liver failure, ALT and AST of around 3,000 or 70 times higher than the upper limit of normal; had a consultation for a possible liver transplant.

After a week in the hospital, he turned

out to be one of the few lucky patients with drug induced liver failure who neither died nor required a transplant.

Because of the incompleteness of the spontaneously reported adverse reaction data currently made available to the public by FDA, it's difficult to accurately count even the reported number of deaths or injuries caused by Rezulin or any other drug. This is because individual adverse reaction reports don't have a unique numerical patient identifier which would allow several reports to be determined to be just follow-ups on the same patient.

As a result, it's possible to over match these reports and under count, assuming what are actually several different patients appear to be the same or the reverse. The fault lies with the cumbersome and difficult to use format FDA is now using to supply data to the public.

Compounding this uncertainty is the widely agreed upon under reporting which may result in as few as ten percent or even one percent of cases which actually occur being reported to FDA.

With these caveats in mind, our estimates of liver deaths from Rezulin up through the beginning of February of '99, with the help of former FDA

pharmacologist Elizabeth Barbaham and Dr. Larry Sasich on our staff, who did a lot of these analyses, 43 deaths, including American and Japanese cases, from liver toxicity from this drug.

Although Warner-Lambert has stated there have been no new liver deaths since the July relabeling, this statement appears to be clearly false.

In addition to the deaths, there are several additional cases of American patients who had liver transplants and survived, making an estimated 45 to 50 cases of liver failure, deaths and transplants apparently caused by Rezulin. An estimated additional 60 or more patients who neither died nor had liver transplants were hospitalized in whom there is evidence of liver damage.

By June 5th of 1998, according to a February 19th, 1999, several weeks ago, letter published in the Annals of Internal Medicine by FDA endocrinologist Dr. Robert Misbin, quote, FDA had received 560 reports of troglitazone associated hepatotoxicity.

Now just a little brief discussion of incidence. The best and possibly only source of information concerning the incidence of liver damage

from Rezulin comes from the company's own 2,510 patient randomized clinical trials prior to approval. Of these 2,510 patients, 48, or 1.9 percent as Dr. Bilstad mentioned before, had abnormal liver tests of three times or greater of the upper limit of normal, which is 40 as opposed to .6 percent getting placebo having this much elevation.

Treatment was discontinued in 20 of these patients because of the tests, but in none of the patients getting placebo. Two were jaundiced; two had liver biopsy. In 18 of the 20 cases, the patients were described as having, quote, liver injury, end quote, of a hepatocellular type.

Although information about the 1.9 percent of patients with liver test abnormalities is mentioned in the FDA approved label for the drug, the following subgroup analysis is not. Ten of the 2,510 patients, or one out of 250, had an enzyme elevation of more than ten times the upper limit of normal, in other words, greater than 400, and five of these had enzyme elevations of more than 20 times normal, or greater than 800.

I would estimate that even if one-fifth of these patients in the real world with the highest enzyme elevations, most of whom are not being

adequately monitored as I'll discuss in a minute, instead continue on the drug because it is not known they're developing a toxic reaction, there may be as many as one out of 2,500 could possibly develop hepatic failure, fatal or requiring transplants in most cases unless the device which we heard about is better than I'm skeptically thinking it is.

(Laughter.)

DR. WOLFE: The real world of medical practice is unlike the artificially vigilant circumstances of the clinical trial where the drug was immediately discontinued in those with the worst abnormalities, more than 20 times normal, because of the close monitoring, and all recovered.

Although this clear evidence of Rezulin hepatotoxicity was known to the company prior to marketing and was eventually published a year ago in the New England Journal, it was not discussed at the December 1996 FDA Advisory Committee meeting in which there was a unanimous recommendation to approve the drug.

In addition, briefing materials handed out by Warner-Lambert to members of the Committee were dismissive of liver toxicity, claiming in those studies reviewed, not all of the 2,510 patients at

that point, that the incidence of elevations of liver tests above normal, quote, was lower for troglitazone than for placebo, end quote, page 90 of the handout, and the text concluded that, quote, elevations meeting threshold criteria for clinically important changes, more than three times normal, occurred at a similar incidence in both groups, troglitazone/placebo.

Given the findings described in the published article about the one out of 500 patients in the randomized trials who developed severely abnormal liver tests, greater than 20 times above normal, and liver damage demands explanation why no requirements to do liver tests was made in Rezulin's initial labeling and why such recommendations were to wait until it had been on the market for seven months and many people were already starting to die of predictable liver failure.

Evidence of serious noncompliance with liver tests. We have obtained data on the prescribing patterns and liver functions, AST, from an academic teaching hospital and medical center. Actual testing was compared to the amount of testing required by the label at the time Rezulin was first prescribed for each patient.

There were a total of 160 patients

prescribed Rezulin through the beginning of March 1999. Of these, 69 were first prescribed the drug prior to the first relabeling in late October of '97 and so were not subject to any testing requirement when they began using the drug.

Of the remaining 91, only 36, or 40 percent, had even a baseline liver function test. Among the 40 patients prescribed the drug after the third and most recent relabeling, it was still 40 percent. Only 40 percent had a baseline test.

I notice there's a little improvement in the data that was just handed out that the FDA is going to present, but it is still pretty pitiful.

At the time of the first relabeling, liver function test -- late October -- was recommended three times in the first month. Then it was escalated to the point where in the first six months it's now recommended seven times.

To repeat, the overall compliance with the baseline testing requirement was dangerously inadequate, only 40 percent of 91 patients who were started on the drug after liver testing was added to the label getting a baseline test.

Only one of 26 patients, or four percent, who were taking the drug for at least six months or

more after the liver testing requirements went into effect were in full compliance with the requirements for testing after baseline.

A necessary precondition for a labeling requirement to reduce toxicity is that the labeling requirement must be adhered to. This has clearly not been the case. The same lack of compliance with labeling was seen with Duract, also an hepatotoxic drug, and Posicor, leading to their withdrawal from the market.

Cardiac toxicity. In a September 1997 memo from FDA Diabetes Group Leader Dr. Alex Fleming, there's a section entitled "Troglitazone Continues to Carry Concerns About Fluid Distribution Among Body Tissues and Cardiotoxicity."

It states, quote, troglitazone is a member of a class of compounds that have been associated with cardiac toxicity. In Study 032, 15 patients, or four percent, on troglitazone as opposed to none of placebo developed peripheral edema. One patient on the drug developed pulmonary edema, which is evidence of heart failure. It is hard to believe that patients with cardiac, liver, or renal disease would not be adversely affected by the drug, end quote.

In reviewing the spontaneous adverse

reaction reports filed with the FDA, we found a total of about 50 patients with heart failure, including six patients who died with heart failure who were taking the drug.

Evidence that others have decided Rezulin is not necessary. Dr. Joseph Lowenstein is an endocrinologist for years at Case Western Reserve University School of Medicine and Meridia Hospital, and now Professor of Medicine at the School of Medicine at Texas Tech Health Sciences Center. He was a member of your Endocrine and Metabolic Advisory Committee from 1980 to 1984 and Chairman of your Committee from '82 to '84.

In response to my question to him about troglitazone, he replied on March 11th, a copy is attached, quote, "You asked me if the removal of troglitazone from the market would impair my ability to provide good care for diabetic patients. My answer is unequivocally, no, it would not. I see a large number of diabetic patients in our faculty and resident clinics, and I have not seen a single patient in whom I thought troglitazone was essential. While troglitazone appears to increase tissue sensitivity in insulin, the published data fail to convince me that its benefits outweigh its risks of fatal liver

toxicity. For this reason I do not prescribe the drug, and when I see a new patient who is already taking it, I discontinue it."

Dr. Lowenstein is hardly alone. Group Health Cooperative of Puget Sound in Seattle, one of the largest HMOs in the country, with 450,000 patients and 575 physicians, also decided that Rezulin is not necessary for the practice of good medicine and have never had it on their formulary.

To their credit, they also never put the three recently banned drugs, Redux, Posicor, and Duract, on their formulary, thus sparing the patients in their consumer run cooperative of a large number of serious adverse reactions.

In other countries, such as all of the European Union, diabetes patients are all cared for without the use of Rezulin, as it has never been on the market in the rest of Europe and was taken off the market in the U.K. in December of '97 by Glaxo Wellcome, its manufacturer there, because of an opinion strongly shared by the British government that its risks outweighed its benefits.

Although Glaxo has now changed its mind, the British government has not and this week rejected Glaxo's efforts to reintroduce the drug in the U.K.

In our petition to the FDA in July of 1998 to take troglitazone off the market because of hepatotoxicity, we stated, quote, "How many more Americans will have to die or require liver transplants before Parke-Davis and the FDA take action to protect people in this country by banning the drug?" end quote.

It is clear one and one-half years after the label first recommended liver test monitoring that most patients are not getting the recommended number of tests or even the baseline test. It is time for the United States to join with the overwhelming proportion of countries where the drug is not on the market and protect American patients from a drug with no evidence of a long-term benefit in mortality, as mentioned before by Thomas Moore, and clear evidence of relatively short-term increased risk of death from liver toxicity.

I point out that a lot of patients who are started on the drug don't stay on it for a long time because it doesn't work that well or, in combination with insulin, causes more hypoglycemia, not less, and therefore, they are getting risks without any benefits.

It is clear that the, quote, label remedy,

end quote, is not effective for those drugs which are inherently too dangerous to remain on the market, such as Duract, Posicor, and Rezulin. Every additional month on the market for Rezulin means longer duration of therapy for hundreds of thousands of patients with concomitant increased risk of liver damage and possible death or the need for transplantation because of liver failure.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Wolfe.

The next speaker will be Dr. Stephen Clement from the American Diabetes Association.

DR. CLEMENT: Good morning, distinguished panel.

My name is Stephen Clement. I'm an endocrinologist at Georgetown University Medical Center here in Washington, D.C. I'm here today as an official spokesperson of the American Diabetes Association.

I am pleased to be here to present the American Diabetes Association's point of view regarding the use of Rezulin for the treatment of Type 2 diabetes.

I think all of you understand the seriousness of Type 2 diabetes and the enormous

challenges it poses for the health of Americans and the American health care system.

I think all of you know the economic impact this disease has and its growing prevalence. We saw slides of that earlier, and I'm sure you will appreciate the statement made by the Centers of Disease Control and Prevention that diabetes is the epidemic of our time.

Last, I hope all of you know or at least appreciate the fact that relatively few people with diabetes in this country have levels of glycemic control that are equal to or even approach normal glycemia, and we saw some of those slides earlier as well.

Since we now know based on the diabetes control and complications trial and the U.K. prospective diabetes study that glycemic control is related to the likelihood of developing complications of diabetes, it comes as no surprise to health care professionals who must work very hard to help patients achieve the best glycemic control they can.

Many factors influence the ability of a patient to achieve good glycemic control. Today all of us are here to talk about pharmacotherapy. In this regard, the American Diabetes Association's comments

will address two questions.

First, how valuable is Rezulin in achieving glycemic control?

And, second, how should the FDA approach the approval and review process of a drug that is first in its class?

First, how valuable is Rezulin? One answer is to look at the impressive rise in the use of the product since its introduction just a short time ago. Certainly effective sales and marketing have influenced the results seen, but in addition, Rezulin is a drug whose mechanism of action is not shared by any other approved glucose lowering agent, and because of that fact it has afforded health care professionals an important advance in pharmacotherapy.

As a practicing endocrinologist, I often face the fact that the present panel of available medications, including Rezulin, cannot adequately control a patient's blood glucose level. As with the other endocrinologists who presented, I find that for patients who are unable to achieve good glycemic control on other medications or combinations of medications, the use of Rezulin often has a dramatic benefit.

This benefit can be sustained over time,

as well. Therefore, I have always appreciated and greatly valued having available many drugs, each acting in different ways to lower blood glucose.

To that end the American Diabetes Association believes that Rezulin has been a very useful drug for many patients, and its unique mechanism of action has been valuable for countless individuals who for many reasons cannot achieve good glycemic control with the other drugs available. Thus, Rezulin is clearly the major benefit to a great number of patients.

Of course, the benefits of Rezulin must be weighed against its risk, and like all other drugs, we know there are risks with taking Rezulin. The American Diabetes Association cannot speak objectively or quantitatively about the risk or Rezulin, nor can we speak about the extent to which monitoring of liver tests has decreased adverse events. We do not collect or review such data.

We do, however, respect and support the FDA's review process, and we have the utmost confidence in its ability to weigh the evidence and decide appropriately whether the benefits or Rezulin outweigh these risks.

The topic of benefit versus risk brings me

to answer the second and last question which I said I would address, that is, how should the FDA approach the approval and review process of a drug that is first in its class.

Of course, one could answer that question in many ways. For example, the rigor of the review process could be different. Less or more data could be required. The bar of effectiveness could be changed.

Through all of these possibilities, the American Diabetes Association would say that no change is warranted. The approach used now is appropriate and effective.

On the other hand, given the difficulty in effectively treating diabetes and given the shortcomings of all other therapeutic options, the FDA should also factor those variables into the benefit side of the ledger in weighing whether to approve a drug that is first in its class.

In other words, not only is absolute clinical effectiveness of importance, but some consideration on the benefit side should be given to a drug that represents a novel way to treat an intractable disease.

Conversely, if a drug does not have a

novel mechanism of action, a risk-benefit analysis may well lead to a different conclusion. Thus, we believe there cannot be a single risk-benefit ratio at which a drug is approved or not approved or removed from the market. Other factors, such as uniqueness and the benefit of its mechanism of action, must also be taken into consideration.

With regard to Rezulin, we know that this drug is unique, and it's clearly invaluable for many patients. Those facts must be taken into consideration. How many deaths due to this drug diminish this benefit?

The American Diabetes Association cannot answer this question or express an opinion because we do not have all the facts. We trust this distinguished panel and the FDA to make these decisions.

In summary, we can say that diabetes is serious. We can say that Rezulin is uniquely effective, and we know that Rezulin carries a risk of serious adverse events. Today the benefits of Rezulin may outweigh its risks given the other therapies that are available.

In the days to come, our knowledge about the type of physiology of diabetes and its

complications will change, and new therapies and new drugs will become available. At that time, the FDA may need to reassess the benefits of Rezulin, as it should all drugs previously approved to treat diabetes, and the American Diabetes Association has confidence that the FDA has the experience, ability, and proven track record to make these decisions.

Thank you very much.

CHAIRMAN BONE: Thank you, Dr. Clement.

Well, we are doing very well, I want everyone to know, and thank you to all. We came quite close to the scheduled time.

The next presentation will be by Dr. David Graham of the FDA Office of Postmarketing Drug Risk Assessment.

DR. GRAHAM: I have to wait for Proxima to get started. We knew they shouldn't have turned it off.

CHAIRMAN BONE: We're going to have to speak to the devices people about which projector they approved.

(Laughter.)

DR. GRAHAM: Parke-Davis can vouch for the difficulties we've had with Proximas.

CHAIRMAN BONE: Can we do something about

this light? This is shining directly in the eyes of several of the panelists, and I hope something can be arranged so that it won't do that. Thank you.

(Laughter.)

CHAIRMAN BONE: Dr. Graham is always illuminating and probably doesn't need to be shiny.

DR. GRAHAM: Lanh, will we be airborne shortly?

I hope that this technical glitch won't count against my time, Chairman.

CHAIRMAN BONE: I once hear that any truly innovative technology has the appearance of magic, and I wonder if we could have a spell here to make this work.

(Pause in proceedings.)

CHAIRMAN BONE: You know, here's what we're going to do. We're going to eliminate the break that was scheduled for after Dr. Graham's talk unless this is ready immediately and take it now.

We'll be returning. I have 9:50. We're going to start up no later than 10:05, and I really mean start.

(Whereupon, the foregoing matter went off the record at 9:50 a.m. and went back on the record at 10:04 a.m.)

CHAIRMAN BONE: Will all the members of the Committee, the FDA staff, and the audience please take their seats immediately? We're ready to start.

The next presentation will be made by Dr. David Graham of the FDA Office of Postmarketing Drug Risk Assessment, whose technology is now working for him rather than against him.

DR. GRAHAM: Is it all right to begin?

CHAIRMAN BONE: Please, go ahead.

The audience will please either take their seats or leave. Okay? We can't have the speaker, the presentation interrupted by this milling about. So please sit down and listen to Dr. Graham.

Thank you very much.

DR. GRAHAM: Good morning. Thank you, Dr. Bone.

My name is David Graham, and the slide that you see here is an imagine of Jan Vermeer's view of Delpht, and it's here to remind members of the Committee that what follows represents our view, the FDA's view, of the scientific data we have available on the risks of hepatotoxicity with troglitazone.

So I'll provide first some background information on acute liver failure. This slide shows the classification system we use to classify case

reports of liver failure reported to the FDA. This classification system is based on the length of time that it takes a patient to go from the appearance of jaundice to the onset of encephalopathy, which is the defining characteristic of acute liver failure.

All of these acute, hyper acute, acute, and sub-acute, are all part of the syndrome of acute liver failure, but they are substratified by the time it takes a patient to become encephalopathic. The hyper acute is very quick, within seven days; the acute within four weeks; and then the sub-acute going out to 84 days.

It's important to understand that overall, about ten percent of all acute liver failure in the United States is due to drugs other than acetaminophen, which itself causes about 15 percent of all acute liver failure. About 70 percent of acute liver failure is caused by hepatitis viruses.

The mortality rate associated with viral acute liver failure is about 40 to 60 percent. The mortality rate associated with drug induced acute liver failure is about 90 percent.

The clinical features of acute liver failure are characterized by the development of coagulopathy, multi-organ failure, and sepsis. Each

of these is caused by the acute liver failure and is not a cause of the acute liver failure.

Next slide, please. Oops, if you could go back -- I'm sorry -- to the previous slide.

This slide summarizes information from five U.S. transplant centers in the modern era, giving information on basically what is the outcome of patients who are diagnosed with acute liver failure, and what we see is about 75 percent of patients with acute liver failure, if you take either die or transplant; if you take these two numbers and this number and add them together; about a quarter of patients manage to survive their acute liver failure without a transplant.

So that means that there are patients who do recover spontaneously. These are usually patients with lower degrees of encephalopathy.

Next slide, please.

It's also important at this point to talk about acute liver failure in diabetes. The question is: does diabetes account for the reports of acute liver failure we've seen with troglitazone?

This slide is to emphasize that there is no evidence to associate diabetes with the development of acute liver failure. There is a small ecologic

association with chronic liver disease. This is suggested by the national hospital discharge summary, which suggests the relative risk of about 1.3. So that would be about a 30 percent increase in the occurrence of chronic liver disease.

However, there are lots of problems with this estimate. It is confounded by alcohol. Alcohol causes liver disease. Alcohol is also associated with diabetes.

Now, from the United Network on Organ Sharing, we obtained data on the prevalence of diabetes in patients who are registered for acute liver transplantation. Now, these data were facilitated by D.W. Chen and his folks at Division of Transplantation in HRSA.

From that data, we learn that about 4.8 percent of patients who are registered for liver transplantation in the United States over the years 1995 through 1998 had diabetes. That prevalence is no different than that seen in the general population matched for age, gender, and race.

So from that data we conclude that there's no association between diabetes and being sick enough with acute liver failure and lucky enough to be registered for a liver transplantation.

However, if you review the literature on acute liver failure, you will find that in none of these is there any association made with development of acute liver failure and diabetes. So from this we conclude that there is no support in the literature or in available data to implicate that the cases of liver failure seen with troglitazone patients is the result of their diabetes.

We'll now discuss how troglitazone is used in the U.S. population. This first slide is from IMS Health Data, their national prescription audit, and it shows the monthly prescriptions of troglitazone in the United States from the time of marketing in March of 1997 through December of 1998, and what we see is that there was a steady increase in prescribing up through late '97 and then a sort of a leveling off, if you will, of prescriptions. These are monthly prescriptions now.

Total prescriptions to date are about 7.9 million, and we estimate that about 1.23 million patients have been treated with troglitazone in the United States.

Next slide, please.

These data come from IMS Health's national disease and therapeutic index, and it describes the

characteristics of patients treated with troglitazone. What we learn is that about 43 percent of use is in women. So the majority of troglitazone use is in men.

The mean age of a patient receiving their first troglitazone prescription is 61. If you look at the age distribution of how troglitazone is used, about 90 percent of its use is in patients 45 years or older, which corresponds pretty roughly with the demography of Type 2 diabetes.

Next slide, please.

This slide comes from data from United Health Care, which is a large health insurance management plan with which FDA has a cooperative agreement arrangement that allows us to do research in the real world, in real populations, of how drugs are used and what the health consequences and effects of those drugs are.

This study is based on 9,400 patients treated with troglitazone since it came on the market in this database that covers 3.5 million lives in the United States over a geographic distribution of nine states, and what we see is that the number of patients who use troglitazone long term, if you were to take a cross-sectional snapshot December 31st of 1998, that very few patients have continued troglitazone for a

long time. Most of the use of troglitazone is limited to patients who have been on the drug for only a few months.

This slide is shown by number of prescriptions filled. It turns out that the average prescription length is 31 days. So there's very tight correlation, and this is basically one month, two months, up through two years.

And what we see here is that if you go out to this, this is the one-year mark. This next line here is 13 months. Less than 16 percent of patients have been on troglitazone for more than a year, and that's very important for what will follow.

If we could go to the next slide, please.

Okay. We will now discuss the cases reported to the FDA of acute liver failure and other serious hepatic injury with troglitazone. We'll begin with a few definitional slides so that the Committee will be oriented to the approach that we took.

We used the classification scheme of O'Grady published in The Lancet in 1993 of acute liver failure, which we showed in an earlier slide. We measured the interval from the onset of jaundice to encephalopathy, transplant or death as one of the metrics that we use for classifying cases into a

category of hyper acute, acute, or sub-acute.

If the timing of jaundice was unknown, we used the time of onset of other symptoms suggested by hepatitis, or if those weren't present in the report, the date when they stopped troglitazone use as a marker for that onset of jaundice.

Next slide, please.

We also classified cases as probable or possible or less likely. We based our analyses on those cases that we classified as probable or possible. These classifications were based on the presence or absence of other potential etiologic factors.

All cases that we classified as probable we believed had an overwhelming evidence that troglitazone was responsible and not other potential factors.

Two of the concepts that are necessary to understand. One is the concept of rapid riser and the other is the unknown riser. A rapid riser is a patient in whom irreversible acute liver failure developed within 37 days of a previous normal test result. We came up with 37 days because we had the monthly monitoring interval that's been proposed in the labeling, and data on compliance with monitoring

that we will present in a few minutes, we used an operational definition of plus or minus seven days of that 30-day interval.

So plus seven days added to 30 would bring us up to 37 days as the time period of a monitoring interval under current recommended guidelines. So rapid riser is somebody who has a normal enzyme level, and then within that period of time goes from normal to irreversible liver failure.

An unknown riser is a patient in whom the time course of the development of abnormal liver enzymes is unknown simply because monitoring was not being performed.

Next slide, please.

This is an overview of the 43 cases of acute liver failure and the 81 cases of hepatitis that have been reported to the Food and Drug Administration. Of the 43 cases of acute liver failure, 38 of them were probably caused by troglitazone. This is nearly 90 percent.

In the sponsor's briefing document, they mention a number of potential confounding factors that they believe may make these cases too complicated to input causality. If the Committee desires during the question period, we can discuss this. However, we

believe in our judgment and in the judgment of a three to four member panel of FDA reviewers that in every probable case troglitazone appeared to be responsible and other factors played either no role or were of a minor contributory nature.

Next slide, please.

In these 43 cases, we show the outcome in this slide. About 13 percent of patients survived without requiring liver transplantation. The remaining patients required transplantation or died. We had 70 percent of the patient population in this review died from their disease.

This survival rate of 12 percent without transplant is very consistent with the data I presented earlier on the natural history of acute liver failure. If you recall on that slide, however, the overall survival rate for acute liver failure is about 25 percent, but that's taking acute liver failure of all comers.

We're dealing with a subset of that, which is drug induced liver failure, which carries a higher mortality rate and so would be expected to have a lower survival rate. If you recall, the literature suggests that the mortality rate from drug induced acute liver failure is about 90 percent. That would

translate to ten percent survival rate without transplant, which is very close to what we find in our case material.

Next slide, please.

The important message of this slide is that about 75 percent of cases have an extremely rapid time course of onset and progression of this disease, and what's also important to recognize is that for most of these patients jaundice is the first indication that they're in trouble, and by then the horse is out of the barn.

Next slide, please.

The patient characteristics in the 43 cases were that 70 percent of them were women. If you recall from the NDTI data, about 43 percent of use is in women. So this is a possible risk factor, gender. It's the only hint of a risk factor that we found in all of our analyses. The mean age was 63, which is very close, virtually identical to the mean age of somebody who starts troglitazone, 61.

The duration of therapy, on average, was about four months, and you see the range here. We had cases reported at every dose level. We also had cases reported with monotherapy. The number of cases at monotherapy was about 20 percent of our total cases,

and the risk looking -- there was no way to say that looking at the proportion of cases caused -- in patients with monotherapy against those who were on combined therapy, there's no apparent difference. In other words, we don't believe that other treatments that patients are receiving for their diabetes in addition to troglitazone are responsible for the acute liver failure. It's the troglitazone, not the other drugs.

A couple other things just to point out on the previous slide. Jaundice is the first symptom at 62 percent, but by the time people come and present, 90 percent of them are jaundiced. So there are patients who might develop other symptoms of nausea, vomiting, or abdominal pain or malaise, symptoms of hepatitis, who within a short period of time generally then go on to develop jaundice, and that's when they present to the doctor, when the jaundice comes, and 90 percent of them have jaundice at that time.

And as we said before, it's a very quick time from jaundice to encephalopathy.

Next slide, please.

This slide just summarizes for the Committee the initial presenting indication of liver injury in the 43 cases of liver failure. Most were

jaundice. Other symptoms of hepatitis were found in 24 percent.

In 14 percent there were transaminase abnormalities. They were otherwise asymptomatic. In six we don't know what the first indication of liver injury was.

Okay. This slide needs to be focused on paying attention to each bar separately so that they don't relate to each other. Each represents a separate category and a separate idea that I'm trying to communicate.

For a baseline testing among these cases, about 45 percent, 46 percent of the cases, 20 out of 43, had some time of baseline test done, but we were very generous in our definition of a baseline test. Basically if the report said that in the last year or so some test had been done, we considered that baseline.

In the data that I'll show later, our enzyme monitoring study, that is not a definition that we viewed as appropriate for baseline testing.

Monthly testing, there were seven cases out of the 43 where there was some evidence of monthly testing being done, but this is an inflated number for the following reasons. It includes one patient from

an NIH controlled clinical trial that by protocol was required to have liver enzyme monitoring. So you subtract that one out.

Then there were three other cases that were from more general populational sources where monitoring was being done more or less, but there were gaps and breaks in it. So they were not fully compliant.

Only three cases, about 15 percent of what's been reported to us, had full compliance with monitoring.

Twenty-one percent of our cases, nine, had what we define as the rapid rise in liver enzymes. This is people who had normal enzymes and within a month of that presented with irreversible acute liver failure, and then for the bulk of patients, we have no idea what the course of enzyme elevation was.

Next slide, please.

This slide is intended to give the Committee an appreciation for what we mean by a rapid riser. What we show here are the liver enzyme levels and functions and the date when different things happened.

And you can see this patient had a baseline test done on February 5th of '98, an ALT of

20. They started troglitazone a few days later. No monitoring was done until August. In August they had normal testing. The patient went on a vacation, experienced some nausea, had some liver tests done at a hospital. I believe it was in Italy. The alkaline phosphatase was 93. The bilirubin was .6. The patient came back to the States. Five days later, still on troglitazone, became jaundice, presented at the hospital in acute liver failure. This patient became encephalopathic, required liver transplantation, and died.

The time from this normal enzyme to this point of irreversibility was 15 days. It's possible that irreversibility actually occurred within five days.

Next slide, please.

This slide is intended to show the time course in an unknown riser. This is the majority of the patients the case material that we have in hand. The format of the slide is identical to the previous.

This patient began troglitazone on December 1st of '97. Two days later they had a baseline test done. The ALT was called normal. We discovered that the value was 11.

Additional monitoring wasn't done. March

1st the patient became anorexic, presented to their doctor a few days later. The doctor got enzymes, said 252, a little touch of drug induced hepatitis here, six times the upper limit of normal. We'll follow the label. We'll stop the drug. The drug is stopped.

But the process was already irreversible. Within three weeks this patient returns with jaundice, an ALT of 1,400. Two weeks after that the patient is Stage 3 coma, and three days after that a liver transplant.

Next slide, please.

This slide summarized a number of observations that impressed me in reading over the case reports that we had. I was struck by the fact that many patients had long prescriptions, and what this allowed to happen was for patients to continue on the drug and not come back to their doctors to have monitoring performed.

It also allowed doctors to sort of basically forget about these patients and not realize that, oh, that patient is still on the drug. So that was one problem area that I saw in these cases.

Another one is that there is, in general, in the real world a time lag between when a patient presents and has the blood test drawn, when those

results are determined, and then when those results get communicated to the doctor and then to the patient. There's a built in time lag.

Now, that time lag might be as short as a day. It might be as long as a week, and I can't say because we have no evidence that if the time lag were instantaneous that it would make any difference, but the fact is that we have to recognize that there is a time lag, and it's built into the way health care is delivered in the United States.

Another observation was that for most of the patients when they present jaundiced they have enough intelligence to stop the drug. However, there were patients who developed nausea or vomiting or a little bit of abdominal pain and who continued on the drug after the onset of those symptoms. In our previous slide, you see how many patients that was.

This can be compounded by lack of physician awareness of the hepatotoxic risks of troglitazone, and we have one case of acute liver failure in which the patient was on the drug for several months and developed a little bit of nausea and a little bit of abdominal pain. They went to the emergency room to be seen. This is in April of 1998. So it's after three "Dear Doctor" letters and all this