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FOOD AND DRUG ADMINISTRATION

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ENDOCRINOLOGIC AND

METABOLIC DRUGS

ADVISORY COMMITTEE

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P R O C E E D I N G S (10:08 a.m.)

DR. BONE: Good morning. My name is Henry Bone. I am calling to order the meeting of the endocrinologic and metabolic drugs advisory committee. This is the 74th meeting of this committee.

This will be a presentation of the data and rationale for regulatory action regarding the withdrawal from the United States market of rezulin, which is troglitazone, produced by the Parke Davis Pharmaceutical Research Division of Warner Lambert, for the treatment of Type II diabetes melitis.

This has been a very interesting and informative case. I think it will be well worth hearing more about this for all of us.

I will ask the members of the committee, advisors, and members of the FDA contingent at the table to introduce themselves. This will be followed by the meeting statement by the executive secretary, Kathleen Reedy. If we could start with FDA?

MR. GRAHAM: David Graham.

DR. LUMPKIN: Good morning. I am Murray Lumpkin. I am the deputy center director at CDER, FDA.

DR. SILVERSTEIN: I am Janet Silverstein. I am a pediatric endocrinologist at the University of Florida, Gainesville.

DR. AOKI: I am Thomas Aoki, professor of medicine, division of endocrinology, at the University of California, Davis, Sacramento, California.

DR. GENUTH: I am Saul Genuth. I am an ad hoc member of the advisory committee, Case Western Reserve University in Cleveland.

DR. BONE: Henry Bone from Detroit, Michigan, chair.

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

DR. HIRSCH: Jules Hirsch, Rockefeller University in New York, member of the advisory committee.

DR. LEWIS: James Lewis, Georgetown University. I am the guest hepatologist.

MS. KILLIAN: Rebecca Killian. I am a patient representative.

DR. SAMPSON: Alan Sampson, department of statistics, University of Pittsburgh.

DR. BONE: Thank you. Next will be a reading of the meeting statement by Kathleen Reedy, the executive secretary from the FDA.

MS. REEDY: 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 for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 United States code 208(b)(3), full waivers have been granted to Dr Thomas Aoki and Dr. Janet Silverstein.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building.

With respect to FDA's invited guests, Dr. James Lewis has reported interests which we believe should be made public to allow the participants to objectively evaluate his comments.

Dr. Lewis would like to disclose that he serves as a consultant to SmithKline Beecham's advisory board on liver safety of Avandia.

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

DR. BONE: Thank you very much. I think that it

is worth noting that the Uniform Public Health Service has demonstrated an excellent regard for the health of people by having their summer uniform.

I think those of us who wish to remove jackets would probably be excused by the rest, in the interests of comfort, since the room is somewhat warm.

The next part of our meeting is the open public hearing.

Agenda Item: Public Hearing.

DR. BONE: This is a unique feature, as far as I am aware, in all the world for drug regulatory authority, to have an opportunity for public comment.

I think it is something that we should realize is quite a special privilege, in the United States a right, of course.

The people who are going to make presentations are asked to state any affiliations or interests that they may have at the beginning of their presentation.

The first presentation is by Dr. David Weeden(?) of the regulatory affairs department of SmithKline Beecham Pharmaceuticals.

Agenda Item: Presentation by David Krause, MD, SmithKline Beecham Pharmaceuticals.

DR. WEEDEN: Good morning, members of the advisory committee, Dr. Lumpkin, other FDA representatives, fellow

physicians, patients and other interested parties in the audience today.

My name is David Weeden. I am vice president and director of regulatory affairs, North America, at SmithKline Beecham.

I am here today on behalf of SmithKline to show our support for the Food and Drug Administration's position that the newer thiazoladine diones, more commonly known as glitazones, are valuable alternatives for patients with type II diabetes.

Diabetes is a health care condition in crisis. Nearly 15 million Americans have diabetes and 200,000 die every year from this devastating disease, which is the leading cause of adult blindness, kidney failure and non-traumatic limb loss in this country.

Clearly, new advances are needed to help control this chronic illness.

The recent introduction of the glitazone class provides a major advance for people living with diabetes, as these are the only therapies that generally treat insulin resistance, an underlying cause of type II diabetes.

Unlike conditional drugs, glitazones increase the body's sensitivity to endogenous insulin, thereby resulting in improved glycemic control.

Given the vast need in the diabetic community for

new therapeutic options, it is critical that patients and health care professionals continue to have confidence in the safety and efficacy of this class.

It was almost one year ago that this committee reviewed the comprehensive efficacy and safety data for Avandia.

At that time, SmithKline Beecham presented to the committee, in this public forum, efficacy and safety data from their extensive clinical trial program, including a third overview of the hepatic safety profile, which included 4,400 patients and 3,600 patient years of exposure.

Those hearings culminated with a recommendation for approval of Avandia, both as model therapy and in combination with mediformin.

Since the glitazone class is relatively new with a novel mechanism of action, all the drugs in the class, including Avandia, have been under intense scrutiny.

We have continued to work diligently with the FDA to provide information about the expanded clinical trial program, as well as the experience of Avandia in the general diabetes population of the approval.

Ongoing review of post-marketing surveillance data showed a debatable safety program and adverse events that are similar to those that were observed in the clinical studies program.

Today there are approximately 270,000 patient years of experience with Avandia, and nearly one million patients have been treated in the United States.

Three million prescriptions have been written since Avandia's approval one year ago.

Clearly, the advances in medical science pioneered with the introduction of this class of agents have provided substantial clinical benefit for many patients.

Avandia has already made an impact on the lives of hundreds of thousands of patients. SmithKline Beecham reaffirms its position that Avandia is a valuable agent for type II diabetes, and that we are committed to ongoing research in the diabetes therapeutic category and in the diabetes community as a whole.

Thank you for your time and your attention.

DR. BONE: Thank you very much. Each of the speakers in the open public session has discussed their time with Kathleen Reedy, and we will give you time when you have two minutes to go, one minute, and when the agreed time is up.

I want to thank Dr. Wooden for staying well within the time and next go to Dr. Patrick Boyle, who is affiliated with the University of New Mexico Health Sciences Center and the National Institutes of Health General Clinical Research Center at that institution. Dr. Boyle?

Agenda Item: Presentation by Patrick Boyle, MD, University of New Mexico Health Sciences Center, NIH General Clinical Research Center.

DR. BOYLE: Thanks, Dr. Bone. It is a pleasure to have an opportunity to make a brief statement before the FDA's presentation this morning.

I have given my time without compensation to come and try to understand the decision that was reached by the FDA regarding rezulin this morning.

I have spoken at a number of medical education programs in order to teach health care providers how to most effectively use troglitazone, and I was compensated for those efforts.

I am here wearing multiple hats today. First, I am an NIH-funded investigator and scientist who has conducted diabetes research for 15 years.

Second, I am a physician with an active clinical practice focused primarily on the care of patients with diabetes.

Third, I am here to represent myself as a consumer, as an individual who is genetically predisposed toward the development of diabetes, and as a past member of the board of directors for the American Diabetes Association, as an advocate for the 16 million people with diabetes who could not be here this morning.

Certainly no one in this room would disagree that the thiazoladine diones have been a major addition to a very limited pharmacologic armamentarium to treat people with diabetes.

For over 1.5 million people treated with troglitazone and improved their glucose control, the drug was a godsend, and offered many of them their first glimpse at near-normal blood sugar concentrations.

I would like to set the tone of this meeting, again, by reminding you that, during the eight weeks since rezulin's withdrawal from the market, 40,000 Americans have died from diabetes-related complications.

This is the third leading cause of death in the United States and the cost of its woefully inadequate management results in each of us contributing to a collective cost of one in five health care dollars to pay for the resulting complications.

As a physician, I am constantly assessing the risk and benefit ratios of any treatment that I prescribe. I don't, for instance, prescribe cumadin for someone with atrial fibrillation who has a big risk of falling.

I do accept a one in 10,000 risk, though, of spontaneous cerebral hemorrhage from this anticoagulant, even when I monitor that therapy correctly.

I accept a one in 50,000 fatal perforation risk

from a barium enema, or a removal of a benign polyp from colonoscopy.

I even accept that, for the greater good of those who need pain relief, over 700 people per year die of end stage liver disease with an over-the-counter pain medication, acetaminophen, when it falls into the wrong hands and it is combined with alcohol.

As an endocrinologist, I accept a one in 10,000 risk of agranulocytosis and death from the use of bionamids for the treatment of Graves disease.

In my own practice, troglitazone was the ingredient that permitted many of the most complicated patients referred to me to have their first glimpse of the type of metabolic control that would lead to a long-term decreased risk of diabetes complications and longer, healthier lives.

All of this occurred with no toxicity, but then, I prescribed it with adequate monitoring.

Let me tell you two quick stories of patients who were not under my care for their diabetes, whose stories I know quite well.

The first patient was a teacher in a one-room schoolhouse in Minnesota. Her greatest passion in life was reading.

After more than a decade of diabetes that had been

detected late in her life, she lots her sight at age 90 and lived the final five years of her life in the dark, unable to read.

Unfortunately, her diabetes was never treated with more than a sulfonylurea. Then, at that point in time in the 1960s, there was really little else to offer her other than insulin.

in reality, she was assessed to be in adequate control for her age, because her urine didn't show any glucose.

The second case is that of a 75-year-old gentleman who was also never treated with more than a sulfonylurea, and maintained hemoglobin A-1C values just over eight percent, which his primary care provider at Kaiser Permanente also assessed as adequate.

He had been a participant in the Mr. Fit hypertension trials earlier in his life, and his blood pressure was always meticulously well controlled with multiple medications.

Now, I would have enjoyed having him come to speak with you this morning, but he experienced a massive left hemispheric stroke last spring and is currently combined to a wheelchair or bed, and has no language to express himself.

These patients -- my mother's mother and my father -- are parts in the statistics of miserable diabetes care

received by many Americans.

In the past, this issue was largely related to inadequate tools and very limited conventional therapies, and true options like a sulfonylureas and medaformin only helped roughly 13 to 25 percent of the patients to reach optimal glucose control by the end of the first decade of their disease.

Even in combination, these two standard medications help another one third of the patients achieve seven percent hemoglobin A-1Cs, and when insulin is used in a primary care setting, 12 percent of the patients get to adequate levels of glycemic controls.

Each of these options has its risks. For a sulfonylurea, it is about a one in 30,000 risk for fatal hypoglycemia. For medaformin, the risk of fatal lactic acidosis in the ball park of one in 50,000.

We accept those risks because of the improved control over the many complications.

I will listen intently this morning to the FDA's presentation and the panel's questions regarding the deaths from liver failure with troglitazone.

I hope that, if there is a suggestion, that the number of these cases was under-reported, that the panel will try to find out how a patient could experience end stage liver disease and not make it onto a transplant list

or somehow simply be thought of to have experienced liver failure that shouldn't be reported to the FDA.

An elevated LDL concentration or peripheral edema common to the other currently available thiazoladine diones, I can partially understand not being reported as an adverse event, but not death from liver failure, not considering the amount of press that this compound somehow managed to attract.

Let me close by saying that I am all for moving on to better versions of diabetes medications. In the case at hand, I fear that we have thrown the baby out with the bath water.

There were some very special properties of this medication that were just about to be disclosed, the prevention of type II diabetes in women with a history of gestational diabetes, and the retardation of atherosclerosis in patients who did not have diabetes.

I believe many people involved in this decision to remove rezulin from the market may have lost sight of the 240,000 young adults, parents and grandparents with diabetes, who annually succumb to the complications of this disease.

Deaths due to poorly controlled diabetes are not flashy. They are slow, sometimes painful. The media would find it difficult to find them as sexy or newsworthy as

liver failure cases.

The sheer number of these diabetes-related deaths should be revisited at every turn of the presentation today. Thank you for your attention.

DR. BONE: Thank you very much, Dr. Boyle. The next presentation will be by Dr. James Freston of Takeda Pharmaceuticals America. I believe -- if you will state your affiliation, I think you are presenting on their behalf but actually are a professor at the University of Connecticut; is that correct, sir?

DR. FRESTON: That is correct.

DR. BONE: Please go ahead.

Agenda Item: Presentation by James Freston, Takeda Pharmaceuticals America.

DR. FRESTON: Thank you, Mr. Chairman. Good morning, ladies and gentlemen. As was mentioned, I am Dr. James Freston. I am professor of medicine at the University of Connecticut Health Center.

I am a gastroenterologist and hepatologist, and my role here is as chairman of the Actos Liver Safety Committee.

In this capacity, I am reimbursed for my time and expenses and, for the record, I also serve as a consultant to Taft Pharmaceuticals and Proctor and Gamble.

Prior to marketing, Actos, a system of adverse

surveillance for liver dysfunction, was implemented by the sponsors, and the formation of the Actos liver safety board was part of that process.

All reports involving abnormal liver function tests are examined by the liver safety board. This is a panel that operates independently from the company.

The panel is comprised of expert hepatologists, who are all nationally-recognized authorities in this field.

They were hand-picked for an additional reason, and that is because of their special expertise in drug-induced liver disease.

Efforts are made to determine cause and effect relationships in all cases received by the panel. This is a particularly challenging exercise in the case of patients with diabetes, because of the very heavy burden of liver disease borne by these patients with diabetes.

As you are aware, these patients suffer from a high incidence of fatty infiltration of the liver, so-called NASH.

There is an increased incidence of hepatitis C in these patients, as well as a very high incidence of biliary tract disease, particularly gallstones.

In addition, these patients, as you know, take a large number of concomitant medications, both for the control of their glucose and for the management of their

complications.

Of course, there is a background of usage of alcohol in this patient population, just as in other patient populations.

The liver safety board recently concluded its analysis of reports based on 10 months of market experience, based on 1,200,000 prescriptions written for 636,000 patients.

So, that is the patient experience that we have analyzed. The liver safety board's determinations are, very briefly, that there have been no cases of acute liver failure.

There have been no liver transplants, or near transplants, and there have been no liver-related deaths.

The liver safety board also will be receiving information from formal post-marketing studies which the sponsor has initiated, in compliance with FDA guidance. Thank you.

DR. BONE: Thank you very much, Dr. Freston. The next speaker will be Dr. John Buse, who is the director of the Diabetes Care Center, University of North Carolina Medical Center.

Agenda Item: Presentation by John Buse, MD, PhD, Director, Diabetes Care Center, University of North Carolina Medical Center.

DR. BUSE: Good morning. I am grateful to have the opportunity to share my personal feelings with this assembly.

I have been a consultant, have received honoraria, and have received grant support from all five companies involved in marketing thiazoladine diones in the United States.

I have expressed my professional opinion regarding thiazoladine diones on innumerable occasions during the last three years while rezulin was on the market.

I base my positive evaluation on rezulin on years spent as an academician, clinician and patient advocate, as well as a researcher in the field of diabetes.

Hundreds of times, in exam rooms, classrooms, at professional conferences and CME presentations, I have asserted my belief that rezulin is one of the most valuable drugs that we have ever had in our arsenal to fight diabetes.

It was with disbelief and dismay that I heard that it was being voluntarily withdrawn from the market at the request of the FDA.

I have prescribed rezulin to many hundreds of patients since I first participated in clinical trials with the drug in 1993.

Just after the drug was approved, I was worried

about the lack of specific labeling regarding liver function test monitoring.

However, I was reassured by colleagues, for whom I continue to have the utmost respect at Parke Davis, as well as by the FDA position, evidenced in the initial labeling of the drug. Neither felt that monitoring was likely to be of benefit.

Soon after the drug was launched, however, two patients were referred to me with nausea in association with rezulin therapy.

Fortunately, these cases have turned out to be rezulin-associated liver toxicity. Although scary, they were not serious.

Very quickly, at UNC, we adopted a stringent program of screening for pre-existing liver disease and liver function test monitoring. As a result, I believe, we have no further significant problems with rezulin hepatotoxicity.

Furthermore, its efficacy in controlling diabetes were spectacular. Hundreds of patients in my practice had exhausted all other potential treatment strategies for diabetes management.

For the first time in their lives, these rezulin-treated patients' blood sugars were under control. More tangible than the theoretical downstream benefit of their

control of their diabetes, these patients felt well and felt good about themselves for the first time in years.

They were able to sleep through the night without frequent urination, and they developed hope that they could live a reasonably long life without the burden of complications.

It is probably true that the disappointment that many of us feel with the withdrawal of rezulin doesn't compare to the bereavement of the families and friends of the dozens of people who died or required a liver transplant, perhaps as a result of rezulin hepatotoxicity.

Without dishonoring their memories, we must remember three things. We must recall the millions of patients who had a good or even excellent response to the drug.

We should not forget the frequency of death and life-shattering disabling complications which afflict three to five percent of patients with type II diabetes annually, as a result of inadequate control of diabetes, as well as the insulin-resistant syndrome.

We must remember that beneficial therapies are generally not risk free, and patients have suffered fatal complications from all of the medications available for the treatment of diabetes.

In balance, rezulin was a tremendous advance for

my patients and nationally, very likely, saved many-fold more lives than it may have ended prematurely.

On a personal note, as I flew to Washington last night, I experienced feelings similar to those during a flight almost 15 years ago, when I was en route to my best friend's wake and funeral.

Kirk, a young man full of promise and potential, died in a house fire which started when he dropped his cigarette when he dozed off to sleep.

His potential was never realized, just as we shall never see whether the promise of early clinical studies, which suggest that rezulin would reduce cardiovascular end points, would have been realized in larger studies, as well as in clinical practice.

My friends and my deeply regretted that we had not adamantly insisted that Kirk stop smoking. With rezulin, a similar sense of regret haunts me. If only we had been more insistent that liver function test monitoring should be part and parcel of rezulin therapy when the drug was first made available.

If, in 1997, the rezulin package insert had been more like the Actos and Avandia package inserts of 1999, I am convinced that we would not be gathered here today.

Both Kirk and rezulin were taken in the prime of their lives. Kirk made my world a better place and I miss

him.

I am also convinced that the world is a better place for the years that rezulin was in development and available in practice.

At a minimum, we certainly owe the scientists and educators at Sankyo and Parke Davis a debt of gratitude for the tremendous effort that they made as part of the development of rezulin, to help physicians and patients understand the role of insulin resistance in both diabetes and cardiovascular disease.

It is clear that they fundamentally changed the thinking of a generation of health care providers regarding approaches in diabetes management, including the encouragement of a comprehensive approach to cardiovascular risk factor assessment and treatment.

This benefit to our patients will clearly endure and has certainly prolonged life and reduced disability.

The issue remains whether the world is a lesser place without rezulin. Only time will tell. Through extensive study and clinical practice, I am convinced that each of the three thiazoladine diones that have reached the marketplace are moderately different.

The greatest consequence that comes as a result of rezulin's withdrawal is the inability to count on the lessons of 10 years of research and clinical experience,

which suggest that cardiovascular risk reduction is a likely outcome of rezulin therapy.

All of us, health care professionals, pharmaceutical industry executives, the FDA and the media, need to be very careful with the remaining agents.

We should aim to use them responsibly, to think critically, and to be constructive as issues of concern arise.

It is clear that the burden of diabetes is large and the need for effective tools is great. I am hopeful that one or both of the remaining agents will prove worthy of being called a safer rezulin. Thank you again, for giving me the opportunity to share my feelings.

DR. BONE: Thank you very much, Dr. Buse. The next presentation will be by Dr. Lawrence Phillips, professor of medicine at Emory University School of Medicine. Dr. Phillips.

Agenda Item: Presentation by Lawrence Phillips, MD, Emory University School of Medicine.

DR. PHILLIPS: Good morning. I am professor of medicine at Emory in Atlanta. Over the past 16 years, I have received research, advisory board and consultant support from many pharmaceutical companies, including Bayer, Bristol-Mayer Squibb, Pfizer, Clark Davis, SmithKline Beecham, Genentech, Eli Lilly, Census and Novartus.

I have ongoing relationships with many of these companies, including Parke Davis, for whom I am a consultant and advisory board member.

At Emory, I have been engaged in developing programs to improve diabetes management in a variety of inpatient and outpatient settings.

Our published analyses of diabetes care have included both municipal and private patients and demonstrate attainment of standard-of-care goals.

We are also involved in a major effort funded by AHRQ and NIH, targeting primary care management of diabetes in a paradigm of partnership between specialists and generalists.

Thus, my point of view is that of the clinician focused on improving diabetes management, both in my own practice and throughout health care systems.

I speak today regarding the utility of different pharmacologic agents available for the treatment of diabetes in the United States.

I have worked with troglitazone since it became available as an investigative drug and since it came on the market.

I have found the drug to be effective and well tolerated and my patients have not experienced problems with liver damage.

In my view, the side effects of this agent appear to be readily identifiable by screening liver function tests.

My understanding of the national data is that the frequency of liver problems has been greatly reduced by appropriate screening of patients prior to initiation of therapy, and by appropriate monitoring once therapy has begun.

This drug has produced spectacular benefits in diabetes control above and beyond those of other drugs which were available before it came on the market.

Thus, we have had many patients who were able to achieve hemoglobin A-1C levels in the six percent range, who simply could not do this despite use of very complex regimens until troglitazone became available.

Our experience in management of patients with Type II diabetes at the Emory Clinic has involved extensive use of troglitazone.

Hemoglobin A-1C in our patients averages 6.9 percent. This has recently been published in Diabetes Care.

Drugs in other oral agent classes are not comparable to the thiazoladine diones and locus of action and use in managing patients with diabetes.

Our patients need all of these drugs. It is not commonly appreciated just how complex management of type II

diabetes must be, if patients are to obtain the near-normal glucose levels required to give hope that the development and progression of the complications of diabetes can be halted or delayed.

In our published studies, we found that 38 percent of type II diabetes could be managed with oral agents alone, but 54 percent of the oral agent patients required two or more agents.

Another 30 percent used oral agents and insulin, and 26 percent used insulin alone. In patients taking insulin, 42 percent required injections three or more times per day. Good diabetes management is not easy.

The thiazoladine dione class of drugs appears to be extremely useful for patients with diabetes. We have used troglitazone both for glucose control and for benefits to the endothelium and the beta cell as well.

Based on data showing that troglitazone reduces intimal hyperplasia after aortic perturbation with a balloon catheter in non-diabetic animals, we have told our patients, this drug may help reduce blood vessel problems in patients with diabetes.

Based on observations that troglitazone improves the insulin secretory response to glucose after in vitro addition to perfused eyelets from Zucker fatty rats, we have also told our patients that troglitazone may help improve

their insulin secretion as well.

We regard the glucose lowering benefit, endothelial benefit and beta cell benefit of troglitazone as strong.

While the other drugs presently available in this class also have glucose lowering benefit, we do not yet know if their action profile on other tissues will be comparable to that of troglitazone.

Just as the relative benefit of different drugs in this class cannot be known without properly designed, well controlled prospective head-to-head studies, we also need these studies in order to fully understand the side effect profile of the different drugs.

Since they are different biochemically and have different metabolism and tissue penetration, their beneficial effects and side effects may differ as well. We will never have this information if the drug is off the market.

Finally, I need to say that the individuals involved with Parke Davis and other American pharmaceutical companies are forthright and completely professional in their desire to develop and market products which will benefit the American people.

I was one of the first to point out that troglitazone might have a side effect potential similar to

other drugs that are used routinely by American and international endocrinologists, with complications which were serious, but rare.

In my recommendations for screening and monitoring, and my discussions of these issues with Parke Davis, I found them to be completely open and fully responsive and proactive, with nothing but the highest concern for the patient.

Thank you for your consideration and for the opportunity to speak.

DR. BONE: Thank you very much, Dr. Phillips. The next person to present is Michael Hackard.

Agenda Item: Presentation of Michael Hackard.

MR. HACKARD: Good morning. Mr. Chairman, members of the advisory committee, thank you for allowing me to testify about the committee's role in the withdrawal of rezulin from the U.S. market.

My name is Michael Hackard. I am the senior partner in the Sacramento area-based law firm of Hackard, Holt and Heller.

My original plans to speaker also included the idea that I would have some of the people I represent here today.

They couldn't be here. They are all too sick, and I will go into that in a little while.

I am not here to incite you or to show disrespect for the process that you have previously engaged in. I am here to plead that the history of rezulin demands that those who took the drug not be forgotten.

In particular, I am here to request that the makers of rezulin use the same vigorous efforts that they used to market the drug to now inform former rezulin users about the potential side effects, liver damage that they may have from taking the drug.

Prior to today's testimony, I took the time to review prior committee testimony and protocol. I noticed that the witness disclosed any conflicts of interest.

In the spirit of this disclosure, you must know that I currently represent at least four dozen individuals or families that have suffered from the adverse effects of rezulin use, at least eight liver transplant patients, 30 patients with non-alcoholic cirrhosis, and 10 families who lost loved ones from the complications due to rezulin.

At least eight of these cases have already been filed in the federal courts of the United States and the others are being prepared for filing.

The defendants in all these cases are Warner Lambert and Parke Davis.

I am not a disinterested observer. My firm represents these clients on a contingency fee basis. I have

personally met and interviewed a substantial number of our rezulin-injured clients.

To me, this committee's earlier failure to remove rezulin from the U.S. market is not a neutral event. I cannot view it as a simple deferral of rezulin withdrawal until safer drugs came onto the market.

To me, the failure to withdraw rezulin earlier is so entwined with tragedy that I must admit that I cannot think about it without an overwhelming sense of regret.

I see the ruined lives of people who asked me to speak here today, people that I have come to know, fathers who want to see their children graduate from high school, mothers who want to stay alive long enough to see their children grow to early adulthood, and adults and their families who are perplexed by this committee's earlier actions, this government's and this manufacturer's failure to act sooner.

Those well informed may well disdain my tone, and I am sorry for that. After all, 100,000 Americans die every year as a result of adverse reactions to drugs, and up to 2,500 cases of fulminant or sudden hepatic failure may be the result of adverse reactions to medicinal agents.

Properly informed people might well be aware that some drugs, for various reasons -- dose, duration, metabolic effects -- may prove toxic to the liver.

The emphasis here is on proper information. This is where the tragedy of rezulin begins and ends, the failure to inform, the failure to inform patients, the failure to inform you, the FDA, and now, finally, those who were formerly on the drug and are still at risk.

Let us just look at a brief history of this lack of information and the company's possibly disinformation.

There are many places to examine the information provided by the makers and marketers of rezulin, but I am not going to argue a legal case.

If I can convey any message at all this morning, it is this. Please take the time to craft an appropriate protocol for determining the nature and extent of existing liver disease among former rezulin users.

How did this committee, Warner Lambert, and Parke Davis respond in March of 1999, when faced with a body of information confirming the lethality of rezulin to some of its users.

Parke Davis presented testimony that 1.5 million Americans had already taken the drug. Their representatives went on to estimate that the risk of developing liver failure from rezulin had fallen from one -- is that two minutes? Mr. Chairman, I would be happy to wrap up.

I have submitted my testimony. I would also say to you, I think it is rather important that you take the

time to work on a protocol.

There is no way in this world that I somehow pulled 50 clients from around the country, 50 clients out of the 57,000 that were injured by this drug.

I can tell you right now, there are a lot of people out there who have been injured, and there are a lot of people who are not being diagnosed by their primary care physicians. Thank you.

DR. BONE: Thank you, Mr. Hackard. The next is a letter from Dr. Stephen Liggett, professor of medicine, molecular genetics and pharmacology at the University of Cincinnati, and member of the medical advisory board of Genaissance Pharmaceuticals. The letter will be read by Kathleen Reedy, the executive secretary.

Agenda Item: Presentation of Stephen Liggett, MD, Professor of Medicine, Molecular Genetics and Pharmacology, University of Cincinnati.

MS. REEDY: Dr. Liggett writes:

Regulatory authorities and drug developers must take an even more rigorous approach to drug development and review by taking advantage of new technologies that can improve the probabilities that the medication best suited for the individual patient is prescribed.

While it is not clear whether the approaches that I will discuss would have prevented the adverse events

attributed to Rezulin, they nevertheless should be considered in this case and perhaps in all future development strategies for new drugs.

I will focus my remarks on the enormous potential of pharmacogenetic analysis during clinical trials. This technology may allow the identification of metabolic differences in patient groups based on genetic polymorphisms.

The resulting product labeling could facilitate the safe and effective use of a drug by allowing prescribers to anticipate necessary dose adjustments, as well as to identify those individuals for whom the drug should not be prescribed under any circumstances.

Indeed, in some cases, understanding how to adjust dose to reduce toxicity may allow the marketing of a drug that would have an unacceptable level of toxicity, were its toxicity unpredictable and unpreventable.

The 1997 FDA Guidance for Industry on Drug Metabolism/Drug Interaction Studies in the Drug Development Process addresses the issue of genetic polymorphisms in some detail.

"When a genetic polymorphism affects an important metabolic route of elimination, large dosing adjustments may be necessary to achieve the safe and effective use of the drug. Pharmacogenetics already has influenced

therapeutics."

This, of course, may also be important in reducing toxicities caused by drug-drug interactions, since polymorphisms may be predictive of drug half life.

Although I am not aware of any specific pharmacogenetic regulations or policies currently in place, the FDA had incorporated the concept of differential therapeutic effects of drugs in different populations through its recent attention to ethnic, age-cohort and gender issues in clinical research and drug labeling.

FDA acceptance of such distinctions as a means of guiding clinical research and drug therapy can help pave the way for the incorporation of pharmacogenetic variability more broadly through more sophisticated means of assaying genomic diversity.

Thus, I believe that we must move beyond ethnic classifications to a purely genetic means of classifying patients in terms of drug response and toxicity.

Although some genetic polymorphisms are differently distributed amongst ethnic groups, it is apparent that at an individual level, genetic differences permeate all ethnic groups.

Stated plainly, to the extent such population/physiologic differences can be predicted and taken into account in treatment, the drug's overall safety

and efficacy are enhanced.

As I state above, this is already done based on a variety of factors -- age, ethnicity, health status and other characteristics.

Pharmacogenetics is just another -- albeit more sophisticated and powerful -- way of accomplishing the same thing.

Additionally, the ICH Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data refers to "intrinsic" -- including genetic and physiologic -- factors having an impact on a drug's effects.

Such characteristics as clearance by an enzyme showing genetic polymorphism and a steep dose-response curve will make ethnic differences more likely.

We did not know if a pharmacogenetic analysis of adverse events correlated to Rezulin should have identified individuals at risk for the unfortunate cases of liver toxicity.

We do know that genes have been identified that are involved in both the response to, and the metabolism of, Rezulin. Some of these genes have genetic polymorphisms in the general population.

Thus, a worthwhile and achievable goal would be to anticipate potentially pharmacogenetic-related issues that arise during clinical trials and for the FDA to consider

pharmacogenetic technology as an integral part of the drug development process.

This will require pharmaceutical companies to incorporate pharmacogenetics technology in their drug development programs, so that safer, more meaningful and potentially more efficient clinical trials can be conducted, with the ultimate goal of incorporating pharmacogenetic information in drug labeling in order to better serve the public health.

DR. BONE: Thank you very much. The final presentation in the open public hearing session is by David Matthews.

Agenda Item: Presentation of David Matthews.

MR. MATTHEWS: Good morning. Mr. Chairman and members of the committee, I would like to thank you for inviting me to speak today.

My name is David Matthews. I am a partner in the law firm of Abraham, Martin, Nicholas, Solos, Matthews and Frank.

I am an attorney representing former rezulin users. We have cases currently pending and are continually evaluating cases concerning the merits of the users' concerns.

We have literally received hundreds of calls inquiring about representation.

As a disclosure, my financial interests are obviously adverse to that of the sponsor. I also have contingency contracts with my clients.

I would like to briefly speak to the committee about three areas concerning rezulin.

First, what we are seeing and hearing in our offices and around the country is devastating. I hear stories of men and women in the prime of their lives with sudden liver failure after taking rezulin.

I hear stories of family members who lost a loved one after sudden weight gain and death from congestive heart failure directly following the taking of rezulin.

I represent a 14-year-old girl that lost her mother. She was a single parent and the child now has to do without a parent and lives with her grandmother.

The stories are compelling sad. They are also ironically sad, because this catastrophe was preventable.

After looking at thousands of adverse event reports and scouring hundreds of thousands of documents in litigation, which we have been in since October of 1999, it is painfully obvious to me that there were concerns of this drug's safety before its approval.

What I don't believe happened, though, was a full disclosure by the sponsor in order for the committee to make an informed decision.

From the pre-approval adverse action reporting to the clinical trials to the echo study, to a review of the prior committee meeting minutes, the evidence strongly suggests the sponsor did not make a full disclosure.

Because of the obvious conflict between company profits and patient safety, I believe reforms must take place.

My colleague, Dr. Jeb Waitt and I, would propose five suggestions for future new drug applications, hopefully to avoid what happened in this particular case.

Number one, a requirement that the sponsor sign an affidavit under penalties of perjury and civil responsibilities, that they have made an exhaustive and complete search of adverse events in the United States and abroad, whether in a clinical trial or not, concerning the proposed drug.

Number two, each principal investigator should appear before the FDA to report the results and to address questions and concerns about both efficacy and safety. This information, as important as it is, should not be filtered through the sponsor.

The investigators could appear individually or collectively to discuss the matters that they found.

Number three, written disclosure of conflict of interest by both sponsor and FDA officials and principal

investigators participating in trials.

We also believe it would be in order to eliminate any conflict waivers.

Four, absolute personal accountability and liability. Anyone who potentially distorts, manipulate or otherwise deceptively influences data which is submitted to the FDA in support of a drug approval.

Finally, five, all reported adverse events shall be presumed to be causally related to the study drug until proven otherwise by conclusive evidence by an independent panel of qualified experts. Thank you.

DR. BONE: Thank you very much. This concludes the open public hearing section of this morning's meeting.

The next item on our agenda is the presentation by Dr. Murray Lumpkin, a deputy center director for the Center for Drug Evaluation and Research. He is the deputy center director for review management. We will have a moment to boot up.

Agenda Item: FDA Presentation.

DR. LUMPKIN: Good morning. I would like to thank, first of all, all the committee members for taking the time to be here today and to be part of this.

I would also like to thank those of you who came in the open public session. Obviously, you have traveled a long way.

I know there were storms in various parts of the country yesterday and people didn't have a particularly pleasant time trying to get here.

It is very important, I think, to all of us at the agency, and I think to the community at large, that we have the opportunity to have this meeting today.

I know some of the questions that we have been getting from various parties is to why we are doing this. Is this something different, is this something strange. Is there some reason that FDA decided, at this committee meeting, to go back, after this drug had been withdrawn, to have this kind of open discussion.

I think the answer to that question really lies in two facets. First of all, it goes to the basic understanding we have of our relationship with our advisory committee members.

As you know, and as you already heard this morning, this particular committee has been an integral part of the regulatory oversight and the regulatory decision making regarding this drug.

They were there before this drug was approved. They again gave us advice in March of last year relative to whether or not the drug should remain on the market at that point in time.

I think our basic promise to our advisory

committee members has been that, given these circumstances where you are so integrally involved in a drug, and we end up taking a significant regulatory action subsequent to your involvement, we owe it to you to come back at the next meeting, and in this kind of a setting, to walk through the data that we have, to walk through the thought process that we went through in reaching our regulatory decision.

I think not to do that, in many ways, basically disqualifies to some degree, or in some way dismisses the value of our advisory committee and the import that we put on the advice that they give us.

This is a feedback mechanism, this is a feedback loop that we are responsible for giving to them.

I think it is also a feedback loop that we are responsible for giving to the community at large. As you have already heard this morning, and as I know all of you know, this has been an extremely difficult risk management problem for the community at large both for practitioners and patients, for the FDA in its effort to do its regulatory oversight, and I think for this committee.

This is something that has not been easy. There are, as you have heard this morning, very well intentioned, well educated people who have honest differences of opinions about a lot of aspects of this drug and about a lot of aspects of this class of drugs.

The differences of opinion, as you have heard this morning, relate to the benefit of this drug, the benefit of this class of drugs.

It also relates to the safety profile, and where you draw the line. Where, as a community, do you draw the line on your risk tolerance. Where as a practitioner do you draw the line on risk tolerance.

Where as an individual patient do you draw the line on your level of risk tolerance. Those are different questions and different people have to answer them for different communities at different points in time.

I think that is part of the message that you hear today, that people have had, and continue to have, honest differences of opinion as to what the answers to those questions are.

Not to attempt to answer them, not to go forward because we are afraid that we have differences of opinion is, indeed, to give an answer, and that is not the right way to go forward.

We believe that this kind of forum, particularly because we have two more products in this class that are still on the U.S. market, is needed to allow the various perspectives and the various opinions that you have heard and that we know exist in the community at large, to have an opportunity to be presented before the committee, to have

the committee have an opportunity to present their thoughts on this, and to give us advice, and for them to begin to think further about these issues as we go forward, leading from troglitazone, as we go forward in our oversight responsibility for rosiglitazone and pioglitazone.

It really is for those two reasons, again, the promise to our committee and our normal process for dealing with these kinds of situations with the committee.

Secondly, I think the circumstances surrounding this drug this class, and the need to have this kind of an open forum, where people who have differences of opinion have an opportunity to express it, to help us regulatorily and to help the committee scientifically, to plan how we might go forward.

With that as introduction, I would like to spend the next period of time with you, I hope most of you have gotten copies of my overheads. They were on our web site. We put them up yesterday morning on the web site. I don't know exactly how many copies were outside.

What I would like to do is spend time with you as a community at large, and with the committee in particular, going back over the data that we had at different points in time, and the thought processes that we went through in making the decisions that we made back in March of this year.

First, I would like to say a special word of thank you to these particular people from the staff at the center for drugs, David Graham and Lon Green from the Office of Post-Marketing Drug Risk Assessments, and Drs. Bob Misbin and David Orloff from our Division of Endocrine and Metabolic Drug Products, who have been absolutely wonderful in helping me prepare these slides and prepare this particular talk for you today.

As background, as you have already heard this morning, troglitazone, known as rezulin in the United States, was approved by the FDA in January of 1997.

It began marketing in the United States in March of 1997. So, later on in this presentation, when you hear me talking about post-marketing data in terms of quarters of time being on the market, we are beginning our time counting from March of 1997, not January of 1997, but March of 1997, when the product actually was launched onto the market here in the United States.

As you have heard this morning already, prior to the approval of this product by the United States, there was a public advisory committee meeting in December of 1996, at which time the committee voted eight to nothing to recommend to the FDA that this particular product be approved for general marketing in the United States.

This product, because it was the first in a new

class of products to treat what is widely recognized as a serious and life-threatening disease, was accorded a priority review.

That does not mean that it was fast tracked, in that sense, because I know people often use those terms interchangeably, and they should not be used interchangeably.

Priority review basically has to do with the fact that when an application comes into the agency, if indeed we believe that it offers something new to a patient population, something new to the practitioner population that is seen to be a potential public health benefit, we will put the resources necessary to do a review within a six-month time frame as opposed to our standard 10 to 12-month time frame.

Again, these are the review time frames that were agreed with Congress under the user fee act in 1992, and reauthorized in 1997.

We did, indeed, a first cycle review within a six-month period of time and the product was, as you can see there, launched in March of 1997.

It was approximately six, seven months after that point in time that we received the first reports from the sponsor, as they are required to send to us, liver failure, reports of what we define as liver failure, and I will talk

about that definition in just a couple of minutes.

In response to those initial reports of patients who were meeting our definition of liver failure, several risk management initiatives were undertaken, both by the FDA and by the sponsor, and I think all of you are aware of this history.

There were several dear doctor letters that went out. The product was relabeled. There were suggestions made as opposed to ways to monitor for this potential liver toxicity.

In March of 1999, it was decided to bring this issue of ongoing risk benefit, in light of the new safety information about which we, as a larger community were aware, to this committee, and again ask the question, given the knowledge of this new data, do you still believe that for the diabetic community at large, that the benefits of this product outweigh what we now know to be the known risks.

The advice we got from the committee at that point in time is as you can see here on the chart.

Indeed, for concomitant use of insulin by a vote of 11 to one, the committee recommended that, indeed, the benefit did continue to outweigh the risk and recommended that we keep the product available.

The same is true as far as concomitant use with

sulfonylureas. However, they did not continue to believe that use as monotherapy had a positive benefit to risk perspective, and they also had some other ideas for labeling and future study. These were all incorporated into labeling for that product after that point in time.

Shortly after that particular advisory committee, two other products -- rosiglitazone known as Avandia and Pioglitazone known as Actos -- were brought before the committee and were recommended for approval.

Indeed, as was troglitazone, they were approved within a six-month review cycle. The reason these products were given priority review status was, as you will hear later on in my presentation, there were, from the data that were in these product NDA, there were at least signs that perhaps these products would show, with ongoing marketing, that they were safer alternatives to the troglitazone product.

For that reason, it was deemed that they were worthy of a priority review and worthy for the agency to expend the resources to conduct priority reviews for these two products.

So, these came on the market, then, in this particular time frame.

Now, let's talk about the adverse event here that we consider, and what has been the one that most of us

talked about and the most severe concern.

That is this whole issue of what we call liver failure. By our definition of liver failure, and as we have done our analysis of the subsequent data that have come in to the agency, we are talking about situations in which there is hepatic insufficiency that results in either death or transplant or recovery without transplant, after becoming encephalopathic because of the hepatic insufficiency, or recovery after being put on a transplant list.

So, if any of these three right here happened to you, it met our definition of liver failure.

Simply having liver insufficiency, that one began having problems with a coagulopathy was not sufficient alone of itself to qualify for this particular definition, just so we are all on the same page as to what we are talking about subsequently, when we talk about cases of liver failure.

Now, I think it is important to know that, at the time of the approvals and also in review of the NDA subsequently, again, knowing what we learned subsequently, we do not believe that any of the three products -- either troglitazone, pioglitazone or rosiglitazone -- had patients that met this definition in their NDA data bases at the time those NDA data bases were submitted to the agency for consideration for marketing authorization.

Now, let's go to the time frame of the decision to

ask the company to withdraw this product. In other words, we are talking now not about today, but we are talking about March of this year.

We are looking at troglitazone reports in our post-marketing system. These are not reports, again, that were in the NDA data base that came in at the time of requesting market authorization. These are reports -- and we will talk about these particular data to a much greater extent.

At the time that we asked Warner Lambert to withdraw this product from the U.S. market, we had a total of 90 reports of patients that met our definition of liver failure.

These shouldn't be particularly new numbers. These were the numbers that were given out at the time of the withdrawal.

Just as a reminder, remember, this represents 36 months of marketing, from March of 1997 through March of 2000.

Of those 90 patients, 60 we were aware had died without undergoing a transplant. Three had died, even having undergone a transplant. Seven at that point in time were still alive, having undergone a transplant. Ten had recovered without having had to have had a transplant. There were 10 others that the ultimate outcome was not known

to us. We were not able to find out the ultimate outcome at that point in time.

We, at the back of our minds, were thinking these probably represent deaths because, obviously, the great majority of these had, indeed, gone on to die, but we simply could not confirm that at this point in time. So, those were the 90 patients and the outcomes that we were aware of at the time we asked the company to withdraw the product.

Now, again, you have to remember, and we will talk more about the kinds of reports we get in our spontaneous adverse event reporting system.

These 90 were the reports that our reviewers in the post-marketing assessment office, as they went through the reports, as they went through discussions with the physicians that were involved, that were getting further information, that at the end of the day our assessors felt were possibly or probably related to troglitazone at the time of market withdrawal.

Again, looking at March, where were we as far as reports we had regarding Rosiglitazone.

Remember, this represents 10 months of marketing for rosiglitazone, not 36 months of marketing, but 10 months of marketing.

We were aware in our data base of two cases that met our definition. One had died without receiving a

transplant and one had recovered without having to have a transplant.

Again, these two were ones that our reviewers thought were at least possibly or probably related to rosi, at the time of the troglitazone withdrawal.

Finally, as far as the data at that point in time -- March of 2000 -- for pioglitazone, representing eight months of marketing, we had no reports that met our definition.

The question that is coming up before us, at that point in time, as we continued to move on, and the question we were faced with is, we had heard from the committee that, in the face of known hepatotoxicity and known death, that from a community perspective, that they still believed the benefits outweighed the risks, and we concurred with that.

Again, that is a difference of opinion, as all of you know, than our counterparts in Europe did, where they took the product off the market and didn't have availability of this class of drug up until the last couple of months.

Our assessment and the assessment we had gotten from this committee was, for the diabetic community at large, having the availability of this class of drugs was important, and that the benefit of that availability outweighed the risk to the community at large.

The question then comes up, as we have moved on,

as we have continued to learn, do we have a situation now where perhaps one could argue that the benefits of troglitazone no longer outweighed its risks because of the availability of two other products and the question of, indeed, do these other products have a safety profile that is better than, or at least reasonably arguably better than troglitazone.

The other part of the question that one has to remember in trying to look at this particular situation is, what about on the benefits side.

Ca we assume that efficacy is equivalent between these products. Is there any data to make us think that perhaps troglitazone might have some unique efficacy or might have some niche population where, indeed, the benefit would outweigh the risk, and this issue of comparative safety with the other two products might have a different calculus because of the efficacy side.

We were in the process here of trying to look at both of these questions and trying to figure out the answer here and the answer here, before coming to a regulatory conclusion.

Now, how do you compare these. Obviously, these products did not go on the market at the same time. They are not being taken by exactly the same patients.

Clearly, patients are, as you heard in the letter

that Dr. Reedy read into the record, there are different genetics, there are different susceptibilities. There are all kinds of factors that are playing into this.

The question is, how could you possibly start comparing these. What is a legitimate apples to apples comparison in order to try to answer those two questions that I just put up here.

Well, unfortunately, and unfortunately as is usually the case, there are no head-to-head data available, head-to-head clinical data that are trying to assess this particular question.

I think as we get into this further and further, knowing the rarity of this very serious adverse event, the question comes up from the statistical side, how would you ever construct a trial.

What would be the size of a trial that one would need in a more pre-approval kind of adequate, well-controlled trial, to try to detect a difference, if one really exists.

I think most of you can imagine we are talking many, many, many patients to the point of even adding, is such a trial even practical, even though one might think theoretically you could, indeed, conduct such a thing.

The reality was, we were faced with this. We had to move on, we had to make a decision here, and we do not

have head-to-head data that are available.

Well, there are three possible comparisons that we were aware of, and I want to share those comparisons with you, what the data are in those comparisons and what some of the argument for the comparison is and what some of the arguments against the comparison are.

The first one, for lack of a better term, we have named the launch-versus-launch comparison. Now, for those of you who are more visually oriented, like I am, I actually have kind of a graphic example of this, that I will review this on again in just a minute and show you kind of how these fit with each other.

Basically, what we are talking about here in launch versus launch is that we would look, since we had nine months of experience with rosiglitazone from the time it came on the market, that means that you had to start therapy and you got into trouble and met our definition of liver failure within that first nine months of the product being on the market.

So, we would compare the rosiglitizone data base with the first nine months on the market of troglitazone and see what that apple to apple looked like, when you looked at the number of reports of patients that got into trouble.

The second comparison that one could look at is one that, for lack of a better term, we have called the

contemporaneous.

This is a situation. Again, it is the same rosiglitazone data base. It is the nine months of marketing that we had.

It says, instead of comparing back to the 1997 experience with troglitazone, let's compare it to the same nine months experience with troglitazone.

So, it is basically the contemporaneous, patients who started in the last nine months and patients who got into trouble in the last nine months of the troglitazone marketing experience.

Last but least is one called the entire exposure versus entire exposure. This says, fine, we will look at patients who have gotten into trouble and meet our definition of liver failure within the last nine months but, in the case of troglitazone, they could have started any time since launch. They are not limited to just having started at the last nine month time frame.

Basically, obviously again, what we are seeing here is that, in all three of these comparisons, the Avandia data base is the same.

It is the 6-99 through 2000 nine-month time frame, patients who started the drug in that period of time and who were reported to us to have had the onset of their disease that resulted in liver failure within that time frame.

The first one we will talk about, again, is the launch to launch. Rezulin will be 3-97 through 11-97, the initial launch of that product; they started the product here.

Somewhere in here, they had disease onset that ultimately culminated in a report of liver failure.

The contemporaneous, Avandia, same data set, versus the last same time frame, June of 1999 through February of 2000, starting the drug at this point and getting into trouble within that nine-month time frame.

Then, the third one, the entire exposure versus the entire exposure, looks at the Avandia data set and says, fine, we will look at patients who had disease onset in this time frame, but they could have started anywhere back here from the beginning of launch.

Hopefully that makes sense, what we are talking about here, with the three different comparisons.

All right, now again, remember, what we are talking about here are comparisons of data that come from our AERS system, our adverse event reporting system.

These are spontaneous data. These are not clinical trials. These are not data from adequate and well-controlled clinical trials, and people need to remember that, because it is a different kind of data.

What you do with it and what you can deduce from

it really does require that you have an understanding of this kind of data, and a history of using this kind of data to make medical and regulatory decisions.

It is a voluntary reporting system. It is not a registry. There are people who have this misconception that our adverse event reporting system, our spontaneous reporting system is a registry of every adverse event that happens to every American who takes every drug in this country.

It just is not so. That is not what it is. It was not designed to be that. You cannot use it as a registry. That is just one of the fundamental issues.

If people think we need a registry, that is a different argument and one that we can have at a different time.

What the spontaneous reporting system was designed to do was to detect as quickly as possible serious, rare, unexpected adverse events, once a product gets on the market.

These are the kinds of things that happens with a frequency that is rare in the sense that we could not numerically pick it up in a normal NDA marketing application.

Most of our marketing applications, as you know, just like these, had several thousand patients in them. If

something is going to happen with a frequency of one in 50,000, one in 20,000, one in 10,000, we are simply not going to pick it up in a normal, traditional, standard, NDA development program. You can do the math. It is just not there.

So, that is what this system was devised for decades ago, and it is similar to systems in other parts of the world to do one thing, and that is to help us identify as quickly as possible, when these products get out on the market, these very serious, very rare, unexpected kinds of problems.

There is obviously, in this kind of a system that is voluntary, a series of biases that are inherent. There is the reporter motivation. There is what we will talk about, this new drug bias.

What we have learned over the years is that we do get the most reports about a drug in the first year to year and a half of it being on the market. There is a bias to reporting more on new drugs.

After a while, it becomes old news, in a sense, and we don't get the same level of reporting.

Because it is a voluntary system and it is not a registry, there is no real denominator, there is no real numerator. So, you cannot in any way come up with incidence rates or trying to calculate really robust incidence rates

based on these data.

Again, it was not designed to allow you to do that, and to ask it to do that, is asking it to do something that it inherently is incapable of doing.

There is an issue of under-reporting, and the under-reporting is an issue we always have to take into consideration in looking at data that come in, in this kind of a system.

There is always a question of the magnitude of under-reporting. I think we would all agree that there is under-reporting, but is the level, is the magnitude of under-reporting the same when you are dealing with something like severe liver failure and toxicity due to that, or if you are talking about a rash due to a beta lactone antimicrobial.

It is a question that is very, very hard to answer and one that I think people would have, again, honest differences of opinion.

There is also the issue that there are no control groups here. This is, again, not an adequate and well-controlled trial.

There are confounding factors. When you read these reports, when you look at them, you find that patients have a whole host of other things going on with them.

Trying to tease out what you think is possibly or

probably related to this particular drug versus another drug versus underlying disease versus a host of factors that might lead to the outcome, you end up with a question about the veracity of causal attribution.

Again, the down side, as it were, about the spontaneous reporting system.

As I say, as a system it has historically been a very good system for generating signals and detecting rare, serious, unexpected adverse drug reactions, and that is what it did in this case.

It is the system that picked this up. It did, I would argue, what it is designed to do.

In trying to get some idea about the depth or the strength of a report, or a signal that comes out of the system, I think we have to argue it is highly situational.

If what you are looking at is something that has a very low incidence background rate, and you start seeing a host of reports, I think you begin to feel that it is a much stronger signal than something that could be a drug adverse reaction, but it also is seen at a fairly high rate in the background population at large.

Then it becomes, obviously, much more difficult to try to put some strength into the signal. I think the signal we are talking about today is one of these where we think there is not a particularly high background rate.

So, we would feel better at putting some element of strength into the signal as we look at these particular cases.

Again, as I said, we cannot do incidence calculations based on these particular reports. We can only do reporting rates.

Again, as I have tried to point out, i comparison to data that we are used to seeing pre-approval, from adequate and well-controlled trials, people might argue that this is soft data and that is hard data.

In reality, as I have pointed out, in dealing with these kinds of situations, these very rare situations but very serious situations, the reality of being able to use adequate and well-controlled clinical trials to help us answer them becomes somewhat impractical.

These are the kinds of data that we, at the end of the day, have to deal with to make our decisions.

So, let's talk about these two comparisons. The launch versus launch, the Avandia data base versus a comparable experience with troglitazone.

Now, what this is right here is looking at our information regarding the total prescriptions that were written here in the United States during the first three quarters of marketing.

If you look at rezulin, you see it had this kind

of penetration in that first nine months. The first month, for example, 100,000 prescriptions written, the second month 150,000 prescriptions.

Again, these are not cumulative data. These are individual data for each month. By the end of this first three quarters of marketing, they were up around 400,000 prescriptions per month.

Now, this does not equate with 400,000 patients per month. You are obviously well aware that, at some point in here, that people were going back for refills of their prescription. So, we will talk a little bit later about how we try to translate prescription numbers into patient numbers.

If you look at the Avandia experience, during its first nine months on the market, you see what is interestingly almost a superimposable kind of penetration into the U.S. market.

By the end of three quarters, Avandia was almost up to 400,000 prescriptions per month at that point in time.

Again, looking at what was going on at market penetration gives, I think, those people who believe that the launch versus launch is the appropriate comparison, an under-girding that we are dealing, to a great degree here, perhaps with apples and apples.

Now, looking at what kind of experience we had in

the first three quarters, this is troglitazone. These are cumulative data now.

In the first quarter, we had no cases that met our liver failure definition, that the onset of disease did not begin in the first quarter. There were, if you remember, a sum of about 421,000 prescriptions written during that quarter.

By the end of the second quarter, we had two cases in the face of 1.2 million prescriptions having been written. By the end of the third quarter, 14 more cases had occurred, so that now this two had become 16 cases.

Again, these are cumulative. So, we had a total of 16 cases from the launch through the end of the third quarter, that had their onset of disease in that period of time, in the face of about 2.5 million prescriptions.

We believe that, having gone out that far, and knowing the kind of refill profile that this product has, that this represents approximately 800,000 to one million patients.

This just gives you what happened in the fourth quarter and the fifth quarter for reference.

Now, if you look at the rosiglitazone experience, during its first nine months of marketing, you see that we had one case that met our definition that had onset of disease within the first quarter.

That was the same case. We had no cases during the first quarter. So, at the end of the second quarter we still only had one total case.

By the end of the third quarter, we had two total cases, in the face of about a million and a half prescriptions, which we would argue is somewhere between 500,000 or 600,000 patients.

Now, one way of looking at this graphically -- and this is kind of where we found ourselves and what we were looking at data wise.

With troglitazone, remember, there were none in the first quarter, there were two in the second quarter, by the end of the third quarter, we were at 16, and then you see it marching on up to about 40.

I think what you see here is that it was the third quarter of marketing that this particular adverse event really began to manifest itself.

With that amount of market penetration, we began to see onset of disease in these kinds of numbers at that point in time.

The question to us on the launch to launch was, what happens with rosi. What kind of thing are you going to see.

At the end of the first quarter, it would be very hard to differentiate those. At the end of the second

quarter, it would be very hard to differentiate.

The issue before us was, if you get to the end of February of this year, which is the end of the third quarter of marketing for rosiglitazone, are we going to see rosi do the same kind of thing, or is it going to differentiate at that point in time.

You know what the data was. That is what it was at the end of February.

So, for people who were looking at this comparison and saying, this is the legitimate apples versus apples comparison, at the end of February, early March as the reports came in, the argument was made, voila, these products have, in the face of marketing with equivalent penetrations into the market in that first nine months, they have now differentiated themselves.

We couldn't differentiate themselves here. We couldn't differentiate themselves here. Ah, they have now differentiated themselves.

Now, if you tried to convert this to an incidence -- again, remember, these are not hard numbers, we do not have the data to allow us to do hard numbers.

If you look at the 16 in 800,000 patients, if indeed this was 100 percent reporting -- and we do not believe it is, but assuming that it was 100 percent reporting -- you would have a one in 50,000.

If this were 100 percent reporting, you would have 250,000. The point here is that you begin to see this kind of one to five ratio that you will see later on, as we look at some other priors and some other data.

Now, the arguments against the launch versus launch, people would say, this is an unfair comparison because the dynamic in the community was really quite different back in 1997 versus what you see in 1999.

Back in 1997, people were not as aware of the potential for hepatotoxicity that in 1999, when rosi came on the market, they had the advantage. The community had the advantage of knowing the troglitazone experience.

Perhaps people were more aware, more educated about the possibility of hepatotoxicity and perhaps they are acting accordingly.

The issue of monitoring and does the monitoring actually help, and the ability to perhaps select patients more appropriately, I think you heard some of those arguments this morning from people who came in the public session.

These were people who did not believe that the launch versus launch was the most appropriate comparison, saying that perhaps the contemporaneous comparison is the proper way to do this.

In the face of the publicity, there should not be

the perhaps ignorance of association in the community at large that might lead to under-reporting.

People who would argue for the contemporaneous comparison would want you to believe that monitoring, indeed, makes a difference, and that the initiation of appropriate liver monitoring makes a difference in the ability to manage this risk and, indeed, physicians are no monitoring appropriate. This would be the argument that would come forward.

The argument would also say that, because of heightened awareness, that physicians would be better able to select appropriate patients for glitazone therapy, as perhaps they would not have been able to in the first several quarters of marketing with the troglitazone product.

Last but not least, because of this heightened awareness and heightened monitoring, that people would be able to stop therapy earlier when signs and symptoms of liver toxicity begin, and therefore, what you are seeing now is a dynamic in the community as far as the utilization of these products, that is very different from what we saw early on.

I am not saying I agree with that. I am just giving you the arguments, that those who try to present the contemporaneous as the appropriate apple versus apple made.

Now, the arguments against the contemporaneous

comparison. First is, I think those of us who have spent a long time having to deal with the spontaneous reporting data base and the various contingencies that one has with it, believe there is, and the history of this particular reporting system underlies the fact that there is what we call a new drug reporting effect.

Now, I mentioned that a little bit earlier, that, indeed, during the first year to two years of marketing of a drug, that is when we get most of our reports.

Once you get out past that period of time, the interest in reporting, the novelty of reporting, the ability of people to actually take the time and say, I believe it is important for me to report this, because the community doesn't know it, really begins to wane.

The assumption s that the community does know it. This is not new news. It is the new product, the one that people don't know about, that has the novelty and has the excitement and has the drive for people to report, obviously, more often in the first year, year and a half, of marketing.

So, by doing the contemporaneous, the argument against it is that you have set up an unfair element as far as reporting, because you are looking at the zenith of rosiglitazone reporting and you are looking at what might be considered a nadir or close to the nadir of troglitazone

reporting, if one looks at the overall experience that we have had with other drugs with this particular reporting system.

There is also the concern later on, as you get further and further and there is the assumption that the community knows about this kind of an adverse event, that we have found with other drugs that people, because of concerns about liability, choose not to report.

Early on, when the community doesn't know, this is scientifically novel, people need to know about this. Once the idea is out there the community knows about this, then we have seen with other drugs that people tend to, again, go more to the nadir or reporting.

One of the things people have told us about is their concerns about liability, again, not with this drug in particular, but I am talking about the system, the spontaneous reporting system, as a whole.

As I mentioned earlier, because of this situation here and the fact that people had a belief in the community that perhaps rosiglitazone and pioglitazone were going to be safer from a hepatotoxicity perspective, that people be more likely to report rosi because this would be a finding.

This would be news. This would be something new, as opposed to reporting yet another troglitazone. It would not have the same impetus in the reporting community.

One other point on this particular element, that I would like to point out as the argument against. When you look at the two reports we got on rosiglitazone, those were direct reports to us.

Those were the physicians calling the FDA and saying, I want to report something. They did it within the first several weeks after the onset.

I think that made those who felt that this was an inappropriate comparison, it gave strength to this argument that people were more likely to report rosi.

Even though it was only an N of two, both of those the physicians actually called us, as opposed to calling the company and going through the company.

They felt it was novel, it was new, and I think it kind of undergirded this concern about the contemporaneous comparison.

There is this issue of monitoring. We talk about things today, there is this issue that we continue to struggle with, about whether monitoring in this situation is, indeed, of value, or whether monitoring is of value in different situations in different ways.

We also have the issue that was brought to this committee's attention back in March of last year, when we tried to find out, were the physicians doing the monitoring, let alone was monitoring helpful. But were physicians

actually doing the monitoring.

Dr. Graham presented to this committee his data from his looks into various data bases at that point in time, which showed actually a very low percentage of people even initiating doing the recommended liver monitoring and, particularly, over time as people went on month after month and after month and seemed to be doing fine, the amount of liver monitoring decreased.

Then the issue of, indeed, given this particular kind of a liver toxicity, can one really identify a patient. One walks into your office. Yes, there are things that have certain kinds of histories of liver illness or certain predisposing factors.

In looking at many of the patients who had this particular kind of adverse events, they were not patients who had the more typical predisposing factor.

So, there is this real issue of, overall, can one actually identify and select appropriate patients.

Now, some of the data that I think argued against the contemporaneous is, when you looked at those 90 patients that we talked about, those 90 troglitazone patients, there were very few who, in their records that we were aware of, you could actually go back to a point and say, oh, they were on drug and they had normal liver enzymes. There were 12.

Now, of those 12, you could follow and they got

into trouble within a month. Remember, we were doing monthly liver enzymes at this point in time.

Basically, what I think this was showing was that, in many of these cases on which we actually have data that there was a normal liver profile on drug and then they got into trouble, it appears to be, at whatever point in time they are going to get into trouble, there was a rapid rise and they got into trouble very quickly.

Again, it brings into question, does monthly monitoring, if this is what pathophysiologically happens, does monthly monitoring actually give you the ability to say, oh, stop, you have gone too far, or is the die cast once you get to this kind of a situation.

I think the other thing that argued against it, for people who were arguing against the contemporaneous, is that in many cases jaundice was the first evidence of liver involvement.

Again, at the time people became aware of liver toxicity, they were dealing with severe cases with rapid onset, once whatever the trigger was to cause it happened.

Last but not least, the total experience versus total experience situation. I will tell you in just a few minutes why I put this up here.

This is looking at people who have had onset of disease that actually met our definition, and that onset of

disease began within the last nine months.

There were 11 of those patients. Again, there were none if you said the cohort starts with patients who started taking drug within the last nine months.

If they started taking the drug at any time since troglitazone was on the market, and got into trouble in the last nine months, there were 11.

Obviously, rosi has, as it always does, the same data base, the two patients.

I put this up here, because I think there was some confusion in the community with the words that were going out about there being or not being deaths since June.

I just wanted to clarify that it depends on what your cohort is. If your cohort is deaths in patients who only started the drug from June of last year forward, that is a true statement.

If your cohort is all patients who have ever started troglitazone, that is not a true statement. That is the data.

So, the only reason for the total versus total, I think, was to try to clarify for the committee and the community at large perhaps some confusion about whether, indeed, there have or have not been deaths on troglitazone since June of last year.

Now, that is the data. Those are the data. Those

are the comparisons that we had at that point in time.

Looking at those particular data, the arguments for, the arguments against, I think you can deduce where the agency went from a regulatory perspective.

I think we felt, at the end of the day, that the launch versus launch was a more defensible comparison than the contemporaneous.

We felt that once we got the data in house on that third quarter of marketing -- i.e., the end of February -- that indeed you could make the reasonable argument that these products had differentiated.

Now, that was not the totality of the world we were living in. Clearly, those were the data that were driving things, but the question is, what else do we know about these drugs.

Are there other priors. Is there other information that help us to either undergird or not undergird this particular kind of an approach.

I just wanted to share with you just some other data quickly, much of which I know you are aware, because this, again, was the world of data that we were living in at that point in time.

Again, in the clinical trial data bases for all three of these drugs, there were no liver related deaths or transplants in any of the three applications.

However, as you remember from the advisory committee meeting, on rosiglitazone and pioglitazone, there was a hint in the pre-approval data base that perhaps when these drugs got on the market, they would show themselves to have a better safety profile.

This was based, I think, primarily looking on the fact that in the data bases for rosiglitazone and pioglitazone, there were no cases of patients with jaundice, and there was less liver enzyme elevation, again, not head to head comparisons, not good hard data, but just looking at the data from each of the NDA trials.

Again, as you know from troglitazone, there were two patients in the NDA data base that were treated with troglitazone that developed reversible jaundice.

One of those patients had a liver biopsy that was consistent with an idiosyncratic drug reaction.

There was another patient -- not one of those two, but another patient -- who also, for other reasons, had a liver biopsy which was read as consistent with idiopathic drug reactions. This information was in the original approved label for troglitazone.

This one, I don't know if your copies actually came out well on this or not. All I tried to do here was show, looking at one liver enzyme in the three data bases, what kind of situation we had, why people felt that perhaps

these two products would end up with a safer liver profile.

This simply tells you, with troglitazone and placebo and these two were the head to head. This is not a placebo that compared or a placebo that compared here. These were from the troglitazone NDA data base.

The upper level of normal was defined as 34 internationals in this particular clinical development program.

You see the number of patients here, 2,510 on troglitazone, 475 on placebo. You see the percentage of these patients that had certain elevations of ALT, greater than three times the upper limit of normal, greater than five, greater than eight and greater than 30.

You see 1.9, 1.7, .9, .2. There was generally, here, a differentiation between troglitazone and the placebo head-to-head comparison.

Now, I did not put up -- because this slide was getting much too small already -- the placebo arms for rosiglitazone and the placebo arms for pioglitazone.

Suffice it to say, they did not differentiate themselves from their placebo comparative arms. You can see the difference.

These were the number of patients in the rosi arm and in the pia arm here, and .25 percent and .23 percent, .05 percent, .0 percent, .33, .25, .03.

I think, again, there was just a general gestalt, looking at these data, looking at the cases of jaundice, or the lack of cases of jaundice, that people felt, you know, when this hits on the market, when we have experience, this is a very rare kind of thing, but if this is prelude for what we might see in the marketing, we might end up with a safer profile once it hits the market.

Also, when you look at back to the AERS report -- this is not NDA data base now -- the other priors that we had going on, the other data that we had, looking back at AERS report, not at cases that actually met our definition of liver failure, but cases that, indeed, were cases of hepatitis or jaundice, as I said, that didn't meet the previous definition of liver failure, but the patient did get put in the hospital or the physician that reported it thought that this case of hepatitis or this case of jaundice was medically significant or life threatening.

Just looking at those numbers -- these are gross numbers. These are not going through case by case by case sorting it out, trying to figure out is there a relationship or is there not, is this possible, or is this probable. This is looking simply at gross report.

We had about 150 reports in our troglitazone data base total. We have 25 reports in our rosiglitazone base total, as of March 2000.

Again, we were trying to see, how do you equate that, given the exposure difference in the population here versus here versus here.

Again, you see this one to five kind of ratio coming back in yet another parameter.

Just very, very quickly, these again are non-comparative trials. These trials do not give you any way of looking at a comparison of safety of rosiglitazone versus troglitazone.

It just gives you some other information about troglitazone and certain kinds of studies that have been underway that had cases of fatal hepatotoxicity.

The only reason I put these up are, as opposed to the AERS system where we talked about, you really don't have a numerator, you really don't have a denominator, you can't really begin to get a handle on incidence, these do have numerators and denominators, and you can begin to see a case.

These are certain situations. Obviously, there were many, many studies that didn't have cases, but these were some that did have a case that met our definition.

This was data from Parke Davis at the March advisory committee, where they looked at all patients in their population-based studies and had one case that came out of that.

This was the diabetes prevention study at NIH that was stopped after one case of fatal hepatotoxicity occurred there.

So, given these kinds of data, and given where we were at that point in time, these were the conclusions that the agency reached in March of 2000.

One is, yes, we cannot give you an absolute hard, fast incidence rate. We can come up with what we think is kind of a ballpark situation, based on the softness of the data that we have, and based on the modeling that we have been able to do over the years with that particular data base.

I think if somebody asked me, can you give me a ballpark estimate of what the incidence might be, we said, we believe that in the acute situation you are talking somewhere probably in the one to eight to 20 to 50 to 100. Obviously, the confidence intervals would be very, very wide here, but somewhere along that.

What was concerning to us -- this again is based on modeling -- is that as we watched people go out further and further and further, even though they were doing fine, doing fine, doing fine, that looking at it from a population perspective, that the more you were on the drug, the further you went out, there was a concern that, with longer-term use, that obviously the potential incidence began to go

down.

This is one of these ongoing discussion points that exist of, do you have longer term risks as you stay on these products longer and longer.

After you pass a certain point, are you home free. If you are not genetically susceptible and you have made it past a certain point, can you relax on this.

I don't think that question has been answered, and it is something that might be particularly helpful in the discussion as we look at the thioglitazones that are still on the market.

As I say, these are brackets. They clearly could be argued to be much larger.

I think the other take-home point from here is that, given all the data that we have to date, we would argue that whatever the incidence of this is, that it is higher than anything that we could have detected in the clinical trial program, given the size of these clinical trials programs.

We don't have anything yet in the data that would make use think, ah, this should have been picked up in the clinical trials programs.

We should have seen these kinds of patients in the clinical trials programs, in a number that would make us think, ah, this wasn't just one odd situation or one

outlier. Indeed, this was a consistent issue that we needed to be concerned about.

So, that is the safety side of the question. Remember, way back when we started this, we had the two questions.

The other question was, perhaps there is something about troglitazone that is unique. Is there a niche population.

Is there some reason for us to change the efficacy calculus in this particular risk/benefit equation.

This was a question we put to the company. This was a question we put to other experts and said, tell us, do you think there is.

By the time we got to March, we had, before the agency, no consistent evidence that demonstrated that, for the population at large, the glitazones were not equivalent in efficacy.

That, again, is an open question. Perhaps with further study, perhaps looking at other indications, perhaps on individual patients -- and I will be the first to say, since this product has come off the market, I have gotten letters from patients who say, give me my rezulin back; I have tried the others; it doesn't do for me what rezulin did.

I am convinced they are probably right, for

individual patients. We are talking about, for the community at large, looking at the risk/benefit calculus of this particular product.

We have yet to have presented to us consistent evidence that demonstrates that the glitazones are not equivalent in efficacy for the treatment of type II diabetes, for that indication for which they are not approved.

There were, of course, other issues. I mean, the one thing we didn't want to do was say, let's just focus on liver toxicity with rezulin and say, oh, these others appear to be safer.

Do the others have some kind of side effect that rezulin maybe didn't have. So, the calculus would have to take that into consideration.

One of the issues with rosiglitazone and pioglitazone was this issue of fluid retention and congestive heart failure, and whether we were seeing an issue with that side effect with those, that perhaps we might not be seeing with troglitazone, again, altering the risk/benefit calculus.

In looking at our post-marketing reporting, again, looking to see if there were signals within our data base at the time of the March withdrawals, we had no signal in our data base that would lead us to believe that this products -

- rosiglitazone or pioglitazone -- within the world of fluid retention and congesting heart failure, were somehow behaving differently.

So, the conclusion. The agency, putting this all together, with the data that was now available to us with the marketing through the end of February and early March, that we came to the conclusion that, based on those data, we thought it was reasonable that rosiglitazone and pioglitazone appeared to have a better safety profile than troglitazone, and offered patients the safe efficacy benefits for the same indication for which they were approved.

Because of that, we believed and asked the company to take troglitazone off the U.S. market.

We believe that it met the definition of what we call an outmoded drug. I wanted to spend just a little bit of time this last few minutes talking about this concept of outmoded drugs.

I think this is something that, not only as the diabetic community but also as a community at large in this country, is something that we are going to be hearing more about over time.

As our academic institutions, as our technology and as our industry gets better and better at producing drugs that are able to target receptors better, as we are

able to do better with genetics and target patients better, as people develop more and more drugs, we are now getting into a new world.

Drugs that previously had a positive benefit to risk calculus no longer have a positive benefit to risk calculus, in the face of newer drugs and appear to have a better safety profile.

We believe this is the situation with troglitazone. We also give you another example, and that was trophinadine.

One phexophenadine, offering patients the same efficacy profile with what appeared, because of the data, to have a better safety profile, the same thing happened. We asked the company to remove trophinadine from the U.S. market.

I think people are going to see this. Oftentimes we, within the community at large, say oh, my goodness, a drug has come off the market. This is terrible. This is failure of the system. Where did it go wrong.

I would argue that taking outmoded drugs off the market, once the agency and community at large feels that we have a safer alternative, is part of our job, and not to do that would be a failure of the system.

We need to look. We need to look at circumstances surrounding a withdrawal. As we go forward, part of our

mission is to continue to survey marketed drugs that had a positive benefit/risk calculus at the time of approval, and continue to compare them with newer products, from a safety perspective, that come on the market subsequent to their original approval.

With that, I would like to stop, Dr. Bone, and turn it back over to you. Thank you all very much.

DR. BONE: Thank you very much, Dr. Lumpkin, for your lucid exposition. I think that what we may do is modify the planned schedule just slightly.

I think the sponsor of troglitazone had some comments they wished to add, and then we can have some discussion with all the presentations having been made. Dr. Peter Corr from Parke David.

Agenda Item: Parke Davis Pharmaceutical Presentation.

DR. CORR: Thank you, Dr. Bone, and good afternoon. I want to thank you for the opportunity to speak with you here today.

I wish to begin by stating that I am not here to argue why we at Warner Lambert-Parke Davis believe that rezulin should be on the market.

Although we firmly believe that the benefits of rezulin continue to outweigh its associated risks, we respect the FDA's position and do not intend to debate,

certainly in this forum, a decision that, as Dr. Lumpkin indicated and made clear, was far from black and white.

Instead, I am here to confirm that at all times Warner Lambert Company has acted with the health and safety of patients as its first and foremost consideration.

Our company is made up of professionals dedicated to human health, and we would not be in this business if our overriding goal was anything other than that.

The dedicated men and women of Warner Lambert-Parke Davis are devoted to discovering and developing innovative drug products to satisfy medical needs for patients around the world.

We in this room, our families and our friends benefit from prescription pharmaceutical products made by Warner Lambert and dozens of other pharmaceutical firms.

At the same time, we know that all drugs, including all drugs for the treatment of type II diabetes, are associated with serious and sometimes fatal side effects.

Our desire is to discover safer and more effective drugs. We will never cease in our efforts.

What about rezulin? No one can really objectively debate the fact that rezulin provided significant benefits in treating type II diabetes.

Since its introduction in 1997 as the first agent

to treat the principal underlying cause of diabetes -- insulin resistance -- approximately two million patients have benefitted from treatment with rezulin, allowing many to achieve a sustained and long term glycemic control.

As with any drug therapy, we also must consider the risks that may be associated with rezulin. We have the deepest sympathy for any patient and his or her family and friends, when an adverse drug experience occurs.

We are well aware of the human dimension associated with these events, and the effects they have on the lives of patients, their friends and families.

However, as the FDA has explained, we must also accept the potential for side effects, because the benefits of approved drugs are more significant than the risks associated with those therapies, and the benefits of rezulin therapy were, indeed, profound.

Let me turn briefly to the rezulin safety data from the past year.

This advisory committee last assessed the benefit/risk ratio of rezulin of March of 1999, at which time the committee supported the continued marketing of the drug.

During the March 1999 meeting, the committee reviewed the benefits of rezulin therapy, as well as the rare reported severe adverse liver events.

Since the advisory committee meeting in March 1999, and the labeling changes in letters to physicians that followed in June of 1999, there has been a marked reduction in the occurrence of cases of severe adverse liver events for rezulin.

As Dr. Lumpkin presented, there have been on cases of liver failure, including death or transplant, for any of the approximately 220,000 patients -- from our IMS data base it is 220,000 patients, as opposed to what Dr. Lumpkin presented, which was 150,000.

In either case, there have been no cases of liver failure on patients starting rezulin therapy following the last labeling change and letters to physicians in June 1999.

As we continued to monitor rezulin post-marketing safety data, we also reviewed the reported safety information for the two new thiazoladine diones, actos and avandia.

Serious adverse liver events were reported in association with avandia, and other serious adverse events were reported for both of these two therapies.

The mere fact that adverse events were reported for those agents does not mean that they were causally related to the drug.

However, we believe that the data currently available for all of these drugs were insufficient to

conclude that truly safe alternatives to rezulin were available.

We have a different view of the incidence calculations and other estimates, including those related to under-reporting of events reported earlier today.

In part, for this reason, we helped design and sponsor both a retrospective and prospective epidemiological study.

The retrospective data base study in 165,000 patients is designed to assess the background rate of liver disease in the diabetic population.

We intend to continue this retrospective study in order to share this important scientific information with FDA and the medical community.

While the results will have no impact on the availability of rezulin, they will benefit patients with diabetes and the medical community.

Of course, the key study that would address the question of comparative safety was the prospective study, which was designed to evaluate the incidence of adverse liver events in patients treated with rezulin, actos and avandia, respectively.

This study was planned to commence in June of 2000. However, with the withdrawal of rezulin, the study is no longer possible.

This brings us to my final point. It is regrettable that a few media outlets and some individuals who spoke in the public session today, who purport to speak on behalf of patients, simply do not know or care about the facts.

As several practicing physicians expressed earlier today, the individuals most hurt by these inaccuracies in the press were, in fact, the patients.

I would like to underscore our firm belief that we must keep discussions regarding drug safety and benefits on an objective level.

No one benefits from sensationalism and a lack of objectivity. Rezulin is off the market.

There are two other drugs in the same class that have the potential to benefit hundreds of thousands of patients, as rezulin did.

Let's not allow inaccurate and sensationalized media reports to supplant subjective scientific discussion of these or any other drugs. Patients really deserve better.

Let me conclude by saying that we are proud of the efforts and relentless work by dedicated and hard-working employees and outside experts, who provided the advice necessary for the company and FDA to understand rezulin.

We are also proud of a cooperative working

relationship with the FDA and this advisory committee.

We pledge our commitment to patients and physicians to continue our efforts to develop safe and efficacious drugs.

We are confident that through the continued cooperative efforts of the pharmaceutical industry and FDA, we can ensure that continuous therapeutic agents are available to address the many unmet medical needs affecting patients around the world. Thank you for your time.

DR. BONE: Thank you, Dr. Corr. I think we will have discussion from the standpoint of any questions or comments that committee members may wish to make, questions that they wish to address to Dr. Lumpkin or others who have made presentations and then we will try to summarize.

One point I just wanted to mention was that at the time of -- there have actually been sort of two phases to the registration of this drug, if I recall correctly.

The initial indication was for co-therapy with insulin and type II diabetes. It was found that a large number of patients were able to reduce their insulin dosage, for a number of reasons that endocrinologists would be familiar with. This was regarded as quite desirable.

Then, the second approval was actually for combination therapy, if I am not mistaken, with other oral agents. Is that right?

Then, monotherapy was included at that time, and later deleted.

The floor is open if there are comments by members of the committee or questions they wish to address to Dr. Lumpkin or to others. Dr. Hirsch.

DR. HIRSCH: I have one question for Dr. Lumpkin. Obviously, the comparison of rosiglitazone and troglitazone in terms of liver disease was an important consideration in withdrawing troglitazone from the market.

I am wondering, how many of the people taking rosiglitazone had taken troglitazone before? Presumably a large number, but we don't know exactly?

DR. GRAHAM: We have some reports of patients who were previously on troglitazone who then switched to rosi or pio.

For most of the analysis, actually for all of our 90 cases, none of them had been previously on rosiglitazone or pioglitazone, maybe one or two.

DR. HIRSCH: Other way around. Of the rosiglitazone, how many had been on troglitazone?

DR. GRAHAM: Both the liver failure cases had previously been on troglitazone.

DR. HIRSCH: So, you see the problem is an obvious one. The rosiglitazone study is a study of troglitazone survivors.

DR. GRAHAM: Correct.

DR. HIRSCH: Therefore, there could have been a sieve in there that pulled out the rosiglitazone-sensitive people, those who would ordinarily have gotten liver disease with rosiglitazone.

DR. GRAHAM: I think there is a good argument against the idea that you weed the population of susceptibles.

That is, we continue, when you plot out the monthly hazard rate over time, the incidence rate per month of use of troglitazone, that it continues at a high rate that is indistinguishable from the rates during early marketing.

At the time we presented to this committee last March, if you recall, we had cases out to eight months, at least, on troglitazone.

I proposed that we would have cases beyond that. The sponsor proposed that the risk dropped to zero at that point.

Subsequent experience has shown that we do have cases that go out, when using the drug, we have cases of severe hepatitis at three years of use of the drug.

What this suggests is that some event happens. Maybe the host bumps into some other factor that, in combination with troglitazone, sets off the chain of events

that lead to liver failure.

As best we can tell, with the high rate continuing out as high as the eye can see, we don't weed susceptibles. They are constantly regenerating. What makes people susceptible is completely unknown to us.

DR. HIRSCH: That is the important last point. In other words, we are going to have to have a whole bunch of people who never had troglitazone, but start on rosiglitazone.

You are without a very important datum unless you do that.

DR. GRAHAM: True, and to gather that information will probably take several more years.

DR. BONE: Could I ask a related question? That is that it is of some interest, what happened to patients who may have had exposure to troglitazone and perhaps a moderate increase in liver enzyme level, and therefore were taken off troglitazone therapy and switched to rosiglitazone or pioglitazone.

Do we have any information on what happened in such cases? Surely there are a substantial number of such cases. I just don't how well they are identified.

DR. GRAHAM: We don't have reports of patients who had problems on troglitazone and then were switched to the other drug and had something bad happen to them.

We are only going to see that side of the equation. Passive information does not indicate that prior enzymemia on troglitazone predicts a problem on one of the other drugs. We don't have any data on that.

One point, though, about the enzyme levels and stopping the drugs and the like is the fact that the patients who developed liver failure seemed to be very different from the patients who developed drug-induced hepatitis.

As Dr. Lumpkin showed before, we had those rapid rises, the nine out of the 12, where within a month they went from having normal enzymes to being on a course of irreversible liver failure.

We have a number of other patients in whom the troglitazone was stopped when the liver enzymes were only three to five times the upper limit of normal.

Those patients, over the course of a month or two months progressed to liver failure and died. The fact that one stopped the drug when the liver enzymes were relatively low was no assurance that they had survived.

It is almost as though a switch had been pulled or a trigger had been pulled that set off a chain of events that was irreversible.

DR. BONE: We had also the information at the time of the original meeting. I think it was 14 patients who had

rather marked increases in liver enzyme level, of whom half had been discontinued and resolved.

The other half had continued on therapy and the abnormalities had resolved in spite of continued therapy. So, this is another factor that confounds the whole analysis.

DR. GRAHAM: What I think it does, it emphasis the fact that the patients who go on to liver failure are different from the patients who develop hepatitis.

The underlying pathophysiologic mechanisms involved are different, and we don't have a way of distinguishing which patients are going to survive and which ones aren't.

DR. BONE: Thank you. Other questions or comments? Yes, Dr. Lewis?

DR. LEWIS: I would just sort of underscore what you are saying. We don't understand the mechanism of the liver failure in many of these patients.

You are right. Some of them had very high enzymes. They continued the drug and nothing happened.

Some of these rapid risers, that is sort of the definition of acute, fulminant hepatitis. It happens out of the blue and it was bad luck, if you will, that liver enzyme monitoring may not have picked that up.

That is what we see, and some of the other

patients were more subacute, where it happened slowly, you stop the drug.

Unfortunately, there are other examples where you try to stop the drug, but the process is already in place.

A lot of this still comes back to, were the drugs really responsible. As was mentioned, assigning causality is very difficult in many of these cases.

These are complicated cases. The two fulminant failures that you mentioned with rosiglitazone, I have reviewed the data base.

I am not exactly sure -- one of them was one of the published cases. I don't recall off hand if they, in fact, did take troglitazone previously.

If they did, that raises issues of perhaps cross-sensitivity, cross reactivity and what not. Neither of the cases that I believe you are presenting, when we have a panel, as was mentioned, that I am a part of to review these cases, we found alternate explanations for both of those.

You know, what triggers a Medwatch report is different perhaps than a very painstaking analysis reviewing the entire medical record, trying to really understand what causes liver failure in many of these patients.

We are still dealing with mechanisms of liver injury. I will put a little plug in for the NIH conference that is coming up in October, where mechanisms of

hepatotoxicity, in fact, will be dealt with over a two-day period.

There may be a lot of useful information that comes out of that meeting, including genetic testing and a lot of other things, which we may be able to use in the future to identify who is at risk.

DR. BONE: That is certainly timely. Other questions or comments from members of the committee? Yes, Dr. Sampson.

DR. SAMPSON: Dr. Lumpkin, I was just trying to clarify in my own mind the change in incidence of the liver failures on rezulin from the first nine months post-launch to the last nine months of data that you had in the AERS system.

You say that you attribute that primarily to the new drug effect in the beginning that stimulates the responses, and to the fear of liability that decreases responses in the last nine months? Am I understanding you correctly in that?

DR. LUMPKIN: I think those are two factors that play into our experience with the AERS data base as a whole.

We do see over time a decrease in the number of reports. I think it is important to differentiate between a decrease in the number of reports and what you believe is actually going on in the community.

Just because it is not reported doesn't mean it is not going on. That is the hard part. That is the tremendously hard part of trying to deduce facts out of this data base, and the various contingencies that go with it.

I think two things you mentioned -- the new drug effect and the various reasons that people do not choose to report later in a drug's life -- we have no reason to believe that that is different for this drug than has been our experience for other drugs.

DR. GRAHAM: Also, we have good data to show that the new drug reporting effect operates with rezulin and that the level of under-reporting with rezulin is substantial.

The new drug reporting effect for rezulin shows a very high reporting in the first six to eight months. Then it drops off at about a year, to what I would consider to be a very stable and low background.

The under-reporting is demonstrated in two ways, by looking at the highest reporting rate of liver failure in any of the early months of the drug, and then applying that rate to the subsequent months to see what one would have expected, and finding that there is a substantial gap of unreported cases.

In addition, looking at very severe liver toxicity but not to the level of liver failure -- that is, hospitalization for jaundice or severe hepatitis -- compared

to what the clinical trials experience was from the NDA, that would give us an expectation that one percent of the population would have enzyme levels that are 10 times the upper limit of normal.

What we find is, we have got a 30-fold level of under-reporting of severe liver disease that falls short of liver failure with rezulin.

So, we have evidence, based on rezulin itself, that the new drug reporting effect applies and that under-reporting exists.

DR. BONE: Just a question for Dr. Graham. I take your point that the -- when we had our previous discussion, it was somewhat unclear whether the rate at which events occurred would remain constant or disappear altogether.

It sounds like we are continuing to have events as time goes on, but the point you just made about under-reporting really depends, to a certain extent, for that calculation on the assumption that the rate does not decline.

From what I heard you say, it sounds as though the possibility that, although the rate doesn't go to zero, it may not be actually zero.

It sounded as though it was not statistically possible to statistically distinguish the rate declining, but that possibility is not excluded, I gather, by the

outcome, that there is a fairly wide band around that estimate; is that right?

DR. GRAHAM: Yes, there would be a wide band around it. Based on the point estimates, which are your best estimates, they are indistinguishable. They are at a very close level.

You have an incidence rate of 250 per million at the highest point, which is about month eight, and about 180 per million at point 17. Those, I would say in my book, are pretty much the same.

DR. GRAHAM: They are certainly much narrower than the extremely wide estimate that we had when we discussed this in the past, in terms of the confidence interval, I gather. Did you want to say something about what the confidence intervals around those estimates are?

DR. GRAHAM: No, because we don't normally calculate confidence intervals around reporting rates.

The fact is, you have got several factors operating here that actually suggest that the under-reporting of the longer duration cases is probably even greater than for the short duration cases.

DR. BONE: That was the point you were making earlier.

DR. GRAHAM: I mean, we have evidence that the people who call us have cases at 18 months or 15 months.

They didn't want to report them, because they didn't think that somebody who had been on the drug and doing well for 15 months could develop liver failure.

Actually, the longer-duration case reports that we have, those are comments that are right in the report that the physician made.

So, basically, early on you have sort of this temporal association where you say, I have given this person this drug and something happened. You can kind of see, maybe there is a cause and effect.

Then you have a situation where somebody is cruising along and they are doing really well. They are at 18 months and all of a sudden, their liver crumps and you say, it is not the drug; they did well.

We think under-reporting is even worse. That raises the specter that you might even have an interval-specific hazard rate that rises with increased duration of use.

DR. LUMPKIN: The only thing I was going to add was to reiterate in this particular light the report that Dr. Hirsch and Dr. Lewis were making, as we think about going forward, and as we continue to monitor the two products that are out there.

The issues of confoundedness, that are going to be very prevalent, and the large number of troglitazone-treated

patients who are now being switched to the other two products.

In fact, as we are planning our monitoring strategy, we are realizing that we are going to have to divide patients into patients who were previously treated with troglitazone, patients who were not previously treated, patients who were treated for a short duration versus patients who were treated for a longer duration.

It is going to make the ongoing surveillance of these products even more complicated than even this initial surveillance has been, because of the large amount of confoundedness that is going to exist because of the switching that has had to occur. I think those are very good points.

DR. HIRSCH: I am in full agreement with what Dr. Lumpkin has said. There is a great deal of actual advertising, as you know, in the newspapers saying, if you have been on rezulin, there is something else here for you which doesn't have the rezulin effects.

At least, it is implicit in the advertising that this is a safer form of drug. Certainly the FDA action indicates that we believe that it may well be safer.

We really don't know that. I mean, as of this moment, there are sufficient confounders, I believe, that this screening phenomenon of those who got ill on the

troglitazone makes a big problem for us.

What it means is that we have to be very, very sensitive to doing studies of people who, for the first time now, are taking rezulin and watch this group, so that we have this information, and we are just not going to have the answer.

DR. LEWIS: Along those same lines, I think it is going to be very important that we get a handle on the question that you asked.

Can you take this drug over a certain period of time and then the risk drops to zero? We don't know that yet.

I think the patients that have come in, where the patients are allegedly having liver problems 15, 17, 18 months later, those need to be very critically reviewed.

It is very unusual, as you know, for most drugs that cause acute injury to do so outside of a general time frame that is up to, you know, nine or 12 months.

That is where we saw most of the cases that were presented with rezulin. There are drugs that cause chronic injury that builds up over time -- methotrexate and some others -- but that is not acute injury.

We are used to thinking about the risk of a drug sort of disappearing after a certain period of time. That is what monitoring guidelines have been written to reflect,

that we don't continue to monitor very frequently beyond the first year with drugs.

It is then labeled periodically thereafter, whatever that mean, every six months, which is suggesting that the risk does, in fact, decrease.

I think it would be very important, both prospectively and getting a handle on the patients who were on rezulin for a long time, if liver disease was reported, that those cases be fully analyzed so that we know if, in fact, we think it is the drug.

DR. BONE: Further comments or questions from committee members?

DR. HIRSCH: Clearly, what we need is all the studies and ideas that have been mentioned. But what the future holds, though, is probably a much better way of doing all of this, and that is finding out what the mechanism of this damage is and then looking at the pharmacogenetics of this.

That is the next real step, and anything we can do to support that, I think, is going to be enormously important.

DR. KILLION: I wanted to -- as a patient, I actually was on this drug for a period of time. As a representative of patients, I wanted to offer my lay thoughts on the process that is involved in the

consideration of this drug.

I have to say that I am actually encouraged by it. I think it is thoughtful and, imperfect, it really couldn't be otherwise, really.

Diabetes is a serious illness that we deal with, and we accept risk in its treatment. The risk analysis per patient changes with the development of alternatives, obviously.

While I think that these adverse events are tragic, they are not really vain or useless, because they focus us on new alternatives or the need for new alternatives.

They give us opportunities for growth. We learn. They spur new development of drugs that may be safer and address these issues.

I don't think any patient wants to dampen that process. So, I come away from this meeting with more confidence.

As always, my mantra is, informed consent. That is what patients need, that is what they require, and that is the responsibility of everybody.

DR. BONE: Thank you. Are there further questions or comments from members of the committee?

Perhaps I will just take a moment to summarize, then.

We have had a very interesting ongoing case study in risk/benefit assessment, which is really the job of the drug regulatory authorities in the United States, as well as everywhere else.

The advisory committee, of course, doesn't make decisions or give advice. This is a forum for discussing issues.

Ultimately, the FDA officials have to make the decisions about what to approve or disapprove.

We had a very interesting and exciting new drug class introduced a few years ago, and of course, troglitazone was the first drug in that class.

We had a drug class introduced that actually permitted the reduction or elimination of insulin therapy in some patients with type II diabetes who had previously required insulin.

We had a potent sensitization to insulin in patients who were being treated with oral hypoglycemic agents.

So, one of the things that we have to bear in mind with drugs of this class has been, and will remain, that they have a major impact on our ability to control diabetes and reduce the complications of diabetes melitis.

The complications of diabetes melitis were described earlier by one of the physicians who spoke, and I

won't repeat that rather impressive recitation.

The morbidity and mortality of diabetes melitis are enormous. One of the difficulties we have in comparing risks and benefits is, we can identify the patient who had a serious or fatal complication from treatment.

It is extremely difficult to the person who didn't become blind or develop kidney failure. These patients are anonymous.

There is the question of statistical risk reduction rather than individual effects.

We saw something very important and new which turned out to be, as far as the class was concerned, a very important innovation.

We saw emerging, some months after the introduction, as a result of the mechanism that we have for identifying cases -- we have discussed the imperfections and limitations of that method. On the other hand, as Dr. Lumpkin said, it did its job.

We learned that there was an unusual reaction, numerically, an unusual and, in our experience as Dr. Lewis has pointed out, in terms of characteristics of this reaction, somewhat different from drug-induced hepatitis or other acute type of reactions that we know a little more about how to evaluate.

The risk benefit assessment was revisited and

adjustments were made, if you will, in the recognized indications and in the precautions that were advised.

This was done in the context of knowing that two additional drugs in the same class, with similar presumed benefits, were soon to be evaluated and, as you know, a few months later these were evaluated by the advisory committee, at least for safety, and were introduced.

We have had an ongoing process, then, of re-evaluating the risk/benefit relationship. The recent development along those lines were described by Dr. Lumpkin as what one might view as a prudential decision.

It is not one where you had absolute final proof or you knew for sure exactly how the comparative risks would ultimately be between these different drugs or whether there was, in fact, an improvement in the risk of troglitazone in terms of the surveillance. We had alternative explanations for some of the reduced number of case reports.

I think Dr. Lumpkin would probably describe this decision as one where the agency felt that the prudent thing to do under the circumstances was to take advantage of the newer drugs which did not have the association with this complication, and the company agreed with the request to have the drug removed.

It is an evolving calculation. As we have heard, we will never have clinical trial data that will detect this

problem with a practical number of clinical trial subjects prior to the introduction of a drug on the market.

What we can do in clinical trials is evaluate a sufficient number of people to reduce the risk to the point where it is not very high, that some serious event will occur.

We will not be able to reduce the risk to a zero point or even to an extremely rare point. We can get the risk down to where it is one case per several thousand, probably, and not have been detected.

We will all have to take that into account when we review new drugs, and when we think about the ongoing evaluation of drugs after their introduction.

One of the most important things we do in our post-marketing studies, which are, in some ways, less crucial, in certain cases, scientifically, than the pre-marketing studies -- and we make our major decisions about the usefulness of a drug based, of course, on the pre-marketing trials -- but those do give us some opportunity, especially when they are a large trial, to look at event rates.

They also sometimes give us the opportunity, in positive control trials, to compare these rates.

If we are still talking about something very uncommon, the event rates will not be sufficiently high to

give us a reliable estimate, one with narrow confidence intervals.

We are left with, as Dr. Graham points out, the point estimate often is the best estimate, but not one in which a solid basis for comparison can always be made.

I think it is a little bit sobering. I think it is encouraging for the reasons I have described. We have seen an important advance, we have seen an emerging problem.

We have seen, in a way, an alternative solution, and we have seen the evolution of the decision making as we move along through that process.

I want to thank the members of the committee, the people who have presented, members of the FDA, and particularly the executive secretary, Kathleen Reedy, for making the arrangements and organizing the meeting.

I want to close the meeting, adjourn, at this point.

[Whereupon, at 12:50 p.m. the meeting was adjourned.]