we've heard whether there have been any further deaths or transplants since the new monitoring guidelines have been in place, and if there have been, did any of those individuals have symptoms in between the monitoring that should have triggered further monitoring and get the drug stopped perhaps sooner.

This relates to Dr. Graham's definition of these rapid risers, which is simply another way of saying hyper acute or acute fulminant hepatic failure, which occurs out of the blue in somebody whose liver is normal to begin with.

But there's no question that I think monitoring of all the types we're talking about is the only way you can pick up these idiosyncratic events.

CHAIRMAN BONE: Dr. Zerbe, did you have an answer for Dr. Lewis' question?

DR. ZERBE: Well, I think the best way perhaps to answer it, if you don't mind, Paul, would be to refer to your slide on rapid risers.

CHAIRMAN BONE: No.

DR. ZERBE: Oh, I'm sorry.

CHAIRMAN BONE: I meant the question about the -- he had a specific question about whether there have been -- about new cases since the most recent set of guidelines were introduced.

DR. ZERBE: There have been cases since the most recent guideline. The rate appears to have decreased, and there were two questions related. I think the other one was related to whether these individual -- any of the people in that time frame represented this rapid riser or did they actually -- were they just not perhaps monitored or managed according to label.

Again, I think the reference to Paul's slide might be the best. We did go through all of these cases with the FDA. There is some disagreement on some of those cases. I don't know that we want to get into a public debate about the individual cases. That was not our intent. We don't want in any way, shape or form to try to discount the cases, but I think they are complicated cases, and we don't necessarily agree in every situation.

If you would like to do that, we can show that slide, show Paul's slide again, which designated all of those.

CHAIRMAN BONE: If that's going to answer Dr. Lewis' question.

DR. LEWIS: Well, it's more to whether they had symptoms in between the monitoring times that should have alerted somebody under the new monitoring

guidelines to do more monitoring, and they might have been picked up before they became fatal or needed liver transplant.

DR. ZERBE: Paul. I think he'd be the best person to answer that.

DR. WHITCOMB: I think it's fair to say, based on the data we have, that symptoms haven't reliably indicated this problem, although there clearly are many cases where in between blood values we have the person that developed abdominal pain, nausea. We heard about a couple of those cases, and I did not systematically review each case looking at it, but it's quite clear there are a sizable proportion of the cases where symptoms didn't appear that the patient would have gone to the physician for, I think it's fair to say.

DR. ZERBE: It is fair to say, Paul, I believe there was one case in which symptoms actually preceded.

DR. WHITCOMB: Oh, there have been several cases where, I guess --

DR. ZERBE: That preceded actual initiation of the drug. I think that was one of the cases of rapid riser, symptoms such as the one you described.

DR. WHITCOMB: Yes. Well, I guess it's whether the glass is half empty or half full. There is no question there are many cases where there were symptoms present and were ignored and the drug continued. However, I'm taking the most conservative position saying there are definitely cases where things had gotten out of control without at least reported at documented symptoms.

Is that -- Jim, am I close to the market here?

DR. LEWIS: Yeah. I mean we're only dealing with a very few number of patients here where full monitoring was going on, and if you're telling me that symptoms may have not been recognized or weren't present, I mean that's not inconsistent with what we see with other idiosyncratic drug reactions. Not everybody gets symptoms, which is why monitoring is imperfect, but it's about the best we can do.

DR. WHITCOMB: That's right. The only other comment is once somebody becomes jaundice obviously there's no need for monitoring. Everyone is aware they have a problem. So I was referring to symptoms really prior to jaundice and the entire data set.

CHAIRMAN BONE: Right. Thank you.

We'll have a question from Dr. Molitch and then Dr. Braunstein's questions. Dr. Kreisberg. Excuse me. I'm sorry, and then Dr. Molitch.

Everybody will get their question asked. I'm sorry if I got them out of order.

DR. MOLITCH: Well, I'm allowed to go ahead apparently.

CHAIRMAN BONE: Please, go ahead, Mark.

DR. MOLITCH: Okay. I want to come back to Dr. New's and Dr. Lewis' question again because I think this is the crux of the problem that many of us are having at the moment in trying to figure out where we're going here, and that is about the efficacy of monitoring in preventing disease.

And we obviously don't have any kind of prospective randomized study with or without monitoring, and that will never happen, but our understanding from what you've said, I think, is that based on experience with this drug and with other drugs that cause similar types of idiosyncratic hepatotoxicity, that, in fact, if we set up a monitoring program and are able to, in fact, have patients monitored, detect the earliest rise in ALT levels at a two to threefold, whatever level we set, say, two to threefold elevation, and then stop the

drug when that is immediately done, is it my understanding or your understanding that we will largely prevent most cases from going on to jaundice and liver failure?

DR. LEWIS: Yes, that's the understanding, that we'll prevent most cases, not everybody perhaps. Probably the best example is with isoniazid, INH. There was a recent modeling study published in the Annals of Internal Medicine which clearly demonstrated that biochemical monitoring, in addition to the clinical monitoring, prior to jaundice and other things, reduced the chance of developing a fatal INH hepatitis dramatically, and this is not dissimilar. They're both drugs that cause, you know, idiosyncratic disease by some toxic metabolite presumably, and it worked in that instance.

It didn't eliminate it. Nothing eliminates it, but it gets it down to a very low level.

DR. MOLITCH: Can you just put a guesstimate number on that most figure? Does it reduce it by 50 percent, 75 percent, 90 percent? What's a guess?

DR. LEWIS: My guess would be 75 percent or more. You'd be able to pick up, stop the drug, and

not have liver disease progress, and that's from experience with monitoring from other drugs.

DR. MOLITCH: Thank you.

CHAIRMAN BONE: All right. We're going to stay with questions, please, for the Parke-Davis people for now, and then we'll come back.

I've got several people in a row, I think. Dr. Kreisberg, and then we have Dr. Braunstein's list of questions, and we'll get to everybody. Don't worry. Okay.

DR. KREISBERG: I don't mean to beat a dead horse, but I think the screening issue is a very important one for me.

First of all, it seems prudent, I mean, to do something like that. It's also very expensive to have to do that.

On the one hand, the Parke-Davis people tell us that the risk virtually disappears over time, and in fact, with the new labeling and the letters to the doctors, the risk of developing this seems to have fallen considerably from about one in 36,000 to one in approximately 60,000.

On the other hand, the FDA, Dr. Graham says, it doesn't change over time. I mean these people are continually at risk.

And I wonder if you would comment on the following question, is that there appears to be an association between the new labeling changes and the reduction in risk, but you're looking at a different population of patients who may have been on the drug for a much shorter period of time, and is this more apparent than real?

DR. ZERBE: That's a very perceptive question, and that's, of course, one of the challenges that you have when you have new patients coming in at different time intervals in terms of you not only are taking calendar time and impacting it with external things like awareness, but you also have a population, a cohort that's moving out.

We have not done that analysis. It would be very complex. You'd have to look at the individual cases in a lot of detail with both bilirubin and jaundice, as well as death. My guess is the death numbers are too small to actually get a reliable answer to that question.

I think the data, making the assumption that the risk, you know, is falling, we'll even take the assumption that the risk is maintained for the purpose of evaluating the calendar effects. I think the data are very strong that the monitoring and

awareness the "Dear Doctor" letters have had a substantial impact on the occurrence of the events.

I likewise feel though that the information on the risk over time -- granted as you get farther and farther out, whether it's David Graham's model or our model, gets more and more questionable -- it would appear that the numbers are going down, and really with a very small increase at the end, which is related to a very few patients in a very small denominator. That appears to be a pretty clear message from our analysis of the data.

DR. KREISBERG: Thank you.

CHAIRMAN BONE: All right. Now it's time for Dr. Braunstein's questions, which are related questions.

DR. BRAUNSTEIN: Right.

DR. HIRSCH: Excuse me. I had one.

CHAIRMAN BONE: Yes, you'll get yours, too.

DR. HIRSCH: Oh, okay.

CHAIRMAN BONE: This isn't the last question by any means. I did not mean to imply that.

I see from the questions that this is going to be, I think, directly addressing several of the other questions in sequence. So I would regard

these as perhaps helpful in moving us closer to closure on some of these issues, if we can.

Dr. Braunstein, you have a list of five questions here, and I think we're asking both the sponsor and the agency to address these questions; is that right?

DR. ZERBE: Are we prepared to address it, Mark?

CHAIRMAN BONE: We can give you a few more minutes if you want to. You're ready?

DR. PIERCE: Yes.

DR. BRAUNSTEIN: First of all, there are differences in the number of total liver associated deaths that were reported in several other papers that we received. Parke-Davis indicated that there were 70 liver associated deaths. The FDA letter to Congressman Waxman in February of '99 indicated 100. The L.A. Times through information they received through Freedom of Information Act reported on 91 liver associated deaths. Yet we're talking about 35 that was agreed upon by the FDA and the company.

And so the first question I have is: how were the others excluded?

DR. PIERCE: Well, the specific answer to the definitions for attributability would need to be

answered by Dr. Watkins, but I think that the general answer to the question really, the discrepancies between Parke-Davis and the L.A. Times, will have to do with the issues both of timing and the issue of attributability, the definition of attributability.

This shows the situation as of March 5th, 1999. The total number of reported deaths or liver transplants is 131; the deaths with a liver mention or liver transplants, 87; and of course, deaths without liver mention are 44. So this deals with just total numbers of deaths report.

With regard to the ones that mention the liver or liver transplant, there are 12 which turned out not to be liver related, and there are 75 which may be. Twelve of those had insufficient information. Twenty-eight were possible, probably related to Rezulin therapy, as Dr. Watkins indicated, and 35 were unrelated.

Between the 12 and the 28 and the 35, as I said, we've agreed with the FDA that there are 35 that are possible or probably related to Rezulin therapy.

DR. ZERBE: And then just to clarify, the 43 number that the FDA has, if there's any confusion, also includes non-deaths with encephalopathy, which we

have not included in our analysis.

CHAIRMAN BONE: Dr. Graham, if I understand correctly, they're saying that the difference here has to do with whether the deaths are attributed as being possibly or probably drug related as opposed to all cases in which there were both mentioned; is that right?

DR. GRAHAM: I think that that's essentially correct. The FDA numbers, I think, represent what the counts were in our computerized system, and that would include any case that's reported. If the patient had cancer and for some reason or another it was being reported as a liver death or gall stones and they died for some reason, as well as duplicate reports, and then you have to go through those reports and get out the ones that you think are related to the drug.

DR. BRAUNSTEIN: So the screen is sensitive, but not specific.

DR. GRAHAM: Exactly.

DR. BRAUNSTEIN: The second question has to do with frequency in reporting of the data. Dr. Graham indicated that there didn't appear to be a change, and Parke-Davis indicated that there was a change after the "Dear Doctor" letter.

In fact, Dr. Graham showed a slide. I think it was page 13 of the handout showing actually a continuous line of reporting over the various dates without a blip at the time either the "Dear Doctor" letters came out or the insert changes were made.

DR. GRAHAM: May I comment?

I believe the explanation for the differences between the company and ourselves is that the data the company presented, they changed the baseline of what it is we're talking about. We were talking about cases of acute liver failure. If you look at the slide that they presented, it was all patients reported with jaundice, and if you subtract out those reports of jaundice and then just presented the stuff on liver failure, you'd see that there was no stimulation of reporting of cases of liver failure.

Now, it may be true that there was stimulation of reporting of jaundice. I'm not prepared to answer that. We haven't analyzed our data to answer that, but we can say that based on our analysis we don't believe that there's any evidence of stimulation of reporting of acute liver failure, and that's what is included in our slide.

DR. BRAUNSTEIN: Well, is it possible then that there's no stimulation because you're capturing

almost all the patients with acute liver failure?

DR. GRAHAM: No, I don't think that that's the case at all. I think what it represents is that when you get stimulated reporting, the stimulated reporting is the result of increased reporting by consumers, but not by physicians, and if you look at the acute liver failure cases that have been reported, that physicians aren't stimulated to report for whatever reasons.

I don't know the answer to that.

CHAIRMAN BONE: Thank you.

A response from the sponsor?

DR. PIERCE: Yeah, I think that the data that I showed indicated the effect of publicity on reporting of jaundice and bilirubin. We picked that because there are a lot more cases and so the data is more robust. Obviously there are many fewer cases of death due to liver failure and transplant.

I also showed data that at least the self-reported likelihood of reporting, you know, increases for death and transplant, is somewhat lower for jaundice, but we really take jaundice as a good index at least over time. It's very, as with death and transplant, they're both very recognized, and we show over time a decrease in the incidence of jaundice and

hyperbilirubinemia as well as the incidence of death.

The data that we presented was presented, and the data I showed in the table, were the cases divided by the denominator of new patient starts in each of those periods. I think that we really don't differ a great deal with regard to that with the FDA.

Last Thursday when Dr. Graham and we had a meeting, he did present a slide, examination of reporting rates by time period where he did really a similar calculation. His overall denominators are different because of a different data source. His time cuts are a little different than the ones that I showed.

But he showed the number of patients in the interval and then divided by the number of new -- well, the number of cases in the interval divided by the number of patients who had a start in that interval and showed a decrease in reporting rate per persons of between 4.78 rate per ten to the sixth persons between March and November 1997, falling to a rate of 2.76 in the August -- well, actually 2.36 between December '97 and July '98, and a rate of 2.76 between August '98 and January of '98.

So I think I may have misunderstood the slide as it was presented last week, but I think that

the issue -- there's not a great discrepancy on that point.

CHAIRMAN BONE: I suppose there's a confounding question here as well because if we have now -- if it's true that this is much less of a problem after a year, there would be a dilution effect by those large number of people who have been on the drug for an extended period of time, and that would be influencing the rates.

DR. GRAHAM: Well, if I can make one comment on that, in the sponsor's presentation of their methods, if you notice in the early part of their slide, they mention why their line was sort of flat up there. It's because they were crediting everybody in the plan with an additional month of time being counted in treatment after they had evidence in their system that they were active.

And so rather than the line going sort of down in a linear fashion -- I forget which slide it was of theirs -- it sort of has this two or three-month blip, and then it goes down, and the speaker did refer to what the reasons for that was, but I believe that that introduces an artifact because what you're doing is you're basically crediting time to people that isn't really credited.

Well --

CHAIRMAN BONE: That doesn't respond to mine.

DR. GRAHAM: Well, then I don't understand your question.

CHAIRMAN BONE: Well, we heard that they have 400,000 people who have been on this drug for more than a year.

DR. GRAHAM: Right. We don't -- well, there's two things going on here. One is we based our analysis using a cutoff date of December '98. They've extended their data another quarter, so another quarter of a year, and based it on that. That introduces some difference.

The second difference has to do with how one measures persistency. We looked at an entire population that was under surveillance for the entire time and were able to follow everybody and account for them, and this is the pattern that we saw, and we didn't have to credit extra time to people or make any assumptions, which at least in the description of their methods it seemed like they were crediting people with more time than they actually had on drug.

And what that would do is that would shift your curve over and make it look like you had people

on the drug longer than they were actually on it for.

CHAIRMAN BONE: Well, that might mean that some of these people were on for 11 months instead of 12, but it wouldn't change the point I was trying to ask about.

DR. GRAHAM: Okay. Well --

CHAIRMAN BONE: Let's go on.

Dr. Braunstein.

DR. CARA: Sorry. Could I ask a related question to this before we move on?

I'm curious as to what this chart that you put together on page 13 of your presentation would look like if you actually put death/transplants rather than acute liver failure.

DR. GRAHAM: All you'd have to do is -- I don't know which one that is.

DR. CARA: It's on page 13.

DR. GRAHAM: Okay. The scatter plot. Subtract out five dots. I mean, just sort of pick them.

DR. CARA: There's no difference in --

DR. GRAHAM: No, there's no difference.

DR. CARA: -- death/transplant?

DR. GRAHAM: Right. No.

DR. BRAUNSTEIN: The next really had to do

with this issue of decrease in death or liver failure following the labeling change and the "Dear Doctor" letters. My understanding from Dr. Graham's presentation was that there wasn't any evidence of a decrease. Am I incorrect in that?

DR. GRAHAM: What I was talking about was the hazard rates over time and the cumulative risk over time. In terms of actual reporting rates, I didn't present any data on that.

The data on reporting rates are that if you look at sort of what would correspond to our cohort one, that first time period, that the reporting rates are about like 4.8 per million persons, and if you go into the second time period, which sort of corresponds to the place between the two "Dear Doctor" letters, it's about 2.4, and if you go into the third time period, which goes, say, from August -- you know, from the second "Dear Doctor" letter to the end of the year, that also is 2.4.

And what you seen then so is a decline in the reporting rate. We have done studies on a number of different drugs and shown that the reporting rate of a product drops from the very first year. It just comes down. It's just a function of reporting. So the first year the reporting rates are higher, and

then subsequently the reporting rates become lower.

And we see that with virtually every drug that we've looked at to examine it. So the fact that reporting rates go down doesn't mean that anything has changed in the background population.

And if you're going to say that cases have declined and you're going to say that it's because monitoring has occurred, then you really have to examine whether or not that statement is accurate, whether monitoring has, in fact, occurred.

And our data, we would suggest, says that it has not. So that can't be brought in as a reason to explain it away.

CHAIRMAN BONE: Comments from the sponsor on this question? It seems to me like it's a fairly important question for the Committee.

DR. PIERCE: Yeah. Whether one looks at this issue of the reporting rate either by new therapy starts, and that's what I showed in my slide, or by person-years, which takes into account this variable exposure, the results are the same.

If one does the periods that I showed instead of by new therapy starts, just number of individuals, but by person-years, one gets a value before December 1997 of one in 22,000 patient-years

for the incidence of death due to liver failure/transplant, and after the period you get a rate of one in 44,000. So that's another way to look at it.

I think, you know, the issue of -- of course, nobody knows the absolute level of reporting rate, and for sure we don't know how the reporting rate changes over time. I think you can support any hypothesis by talking about changes in reporting rate over time.

So what we've shown you is the reports over time without making assumptions about changes in reporting rates or the reporting rate.

DR. BRAUNSTEIN: There also seemed to be a fairly large discrepancy between the estimated frequency of liver failure between Dr. Graham's estimate and Parke-Davis' estimate. Dr. Graham's numbers, if I understand the modeling and everything else correctly, indicated that the rate would be one in 1,000 to 2,000 individuals exposed to the drug for six-plus months, whereas the sponsor indicates that it's maybe at the most one in 34,000 patient-years of exposure, and that's a pretty large discrepancy there.

DR. GRAHAM: Right. What the sponsor has done is given you basically their estimation of a

reporting rate, and they don't account for person-time in that analysis.

What we've given basically, that one per 2,000 at six months translates to a person-time rate of 1,000 per million person-years. Now, if you look at the company's data from Table 2 of the briefing document that they sent you where they presented all their population based data -- see, that's the other thing. Our rate comes from -- we're using the population based data from the REACH study, the DPP study, the UHC study, and the modeling that we did was spontaneous case reports that led us back to a very similar rate, and that's where we come up with that estimate.

If you look at that Table 2 from the sponsor's study where they did the aggregate analysis that in my presentation I indicated I didn't think that it was appropriate because it hides certain things about the data, they come up with an estimate there of 290 per million person-years for acute liver failure.

So compare 300 to 1,000. See, it then -- all of a sudden the gap between what they're presenting, which is a frequency count -- it's a reporting count. You have under reporting, and

they've counted all the individuals and somebody on the drug for one week contributes the same amount of weight to the denominator as somebody on the drug for ten years, and so then you get a very different -- you get a very exaggerated difference in where we're coming from.

CHAIRMAN BONE: Obviously we want to hear from the sponsor on this point.

DR. FAICH: Well, let me just take those three sources of estimates. We've already talked about the clinical trials at length, about whether the numerator is two or not two and how certain that number is and what the denominator is, and you've heard my views on that earlier.

I think that the best point estimate from the clinical trials is on the order of one per 5,000 to one per 7,000.

The issue of using person-time as opposed to persons, which is the same one in clinical trials as it is postmarketing, has to do with whether you think that there's a continuing not only risk but a cumulative effect in patients as opposed to an idiosyncratic effect that happens only once per person, whether it happens in the first month or the second month or third month of therapy.

So you have to think about what is the biologic mechanism which would then drive the epidemiologic denominator calculation.

I would submit as you look at the distribution by month of cases, it looks to me like, in fact, they are not continually happening over time; that they do, indeed, tail off in patients who have had four, five and six months of therapy; that that peak is somewhere between three and five months, and that's more suggestive.

It's true that could be a phenomenon of the reporting system, but if you believe that reporting is high, which is actually key to all of this discussion, then the suggestion from the spontaneous reports is that an individual is only susceptible once. So, therefore, you would then count new starts as opposed to person-time, and that is a major difference.

I don't see a biologic compelling reason why you would see this cumulative toxicity in individuals. That's probably the single biggest difference.

Looking at the database issue, the UHC data, we hold, is not yet reliable or useful to look at at this point and is a preliminary probe. So I

would contend the best data to look at, in fact, are the numerator data from reporting and the denominator data from the total number of patients treated, and you can take total numbers of patients treated and then look at treated for X number of months, and we did that, and we displayed those data.

CHAIRMAN BONE: Right. Thank you.

I think we --

DR. BRAUNSTEIN: Does that actually address the last question? He wants to respond to it.

DR. GRAHAM: Yeah, no the --

DR. BRAUNSTEIN: When the injury occurs.

DR. GENUTH: On peak and what happens after that. Well, it's clear from our data that based on the reporting that we have, that the peak we found is at six months, and that we don't have reporting of cases of liver failure beyond eight months. So our last case occurred during the eight months of treatment that we have reported to us.

However, several lines of arguments. One, we know the denominator is shrinking, and so there could be cases out there that haven't developed yet or that it takes longer to develop because you have to accrue enough person time in that exposure period to produce the cases.

A second thing is that from the sponsor's own clinical trials described in their briefing document, they had patients as far out as 18.2 months that had liver enzyme abnormalities that were above the three times upper limit of normal.

What you run into, the problem is that you're talking about a very shrinking denominator and what happens out there. So it's hard to say.

With INH, if you read the literature on INH, the number of cases that occur with INH of fatal hepatitis with extended use is small, but that's because the denominator of patients at risk who are using the drug out that long is also small.

In some of the articles that I've read, authors actually make the comment that the actual hazard rate to patients with extended use may actually be higher than it is earlier on. It's just that most people stop the drugs with six months or three months of treatment.

CHAIRMAN BONE: Anything further from the sponsor on that point?

DR. CARA: That's a very -- I'm sorry.

CHAIRMAN BONE: Please, Dr. Cara, go ahead.

DR. CARA: It's a --

CHAIRMAN BONE: Jose, I was going to let the sponsor finish, and then we have -- I know everybody has questions about these data.

DR. PIERCE: Could we show the next to the last slide in my presentation?

Just to show this again, both for jaundice and hyperbilirubinemia, and this is risk as a function of duration on drug, jaundice and hyperbilirubinemia peak at about three to four months. Death and transplants peak perhaps four to five months and then decline thereafter, and we show both of them to show basically the parallelism between them both. Jaundice and hyperbilirubinemia, this includes all cases, and it's also heading down.

You know, the slide that Dr. Graham showed also showed a similar peak. What this is really -- this is showing the interval specific hazard rate at each interval each month. Dr. Graham showed the slide and explained that the peak interval specific hazard rate occurs at six months and then declines. There are only two more points on that curve because there are no cases beyond that point.

CHAIRMAN BONE: Just for clarification, did I understand correctly that the number of patients who have been on drug for 12 months or more here is

400,000? Is that correct?

DR. PIERCE: That's correct.

CHAIRMAN BONE: Is that agreed, Dr. Graham?

DR. GRAHAM: No, we would not agree with that, with that estimate.

DR. FAICH: What's your estimate?

CHAIRMAN BONE: This sounds like it's probably going to be critical. So let's settle this if we can.

DR. GRAHAM: I don't have my slides right in front of me, but if you look at the slide on the UHC slide, it's early on in the drug use section of my presentation, and it's the slide that shows the falling prescriptions.

Go out to 12 months, and I think it was something like 16 percent at 12 months.

CHAIRMAN BONE: Page 4?

DR. GRAHAM: Well, no. They want to know how many people have gotten the drug for more than a year. Is that the question?

CHAIRMAN BONE: That's what I'm trying to get clear about.

DR. GRAHAM: Right. Well, if you look at that slide and then look at month 13, and that will

show you that percentage is less than 16 percent. So let's pick 15 percent.

Fifteen percent of 1.23 million people are the number of people that we would estimate have used troglitazone for more than a year.

CHAIRMAN BONE: So your estimate is about 190,000.

DR. GRAHAM: Whatever that math works out to.

CHAIRMAN BONE: Is that what that comes out? I think that's about that. All right. So let's say in round numbers 200,000.

And the company has a different set of estimates, I take it, and I believe you said that you based this on pharmacy reports; is that right? Go ahead, please.

DR. WATKINS: Our estimates come from national data sources which samples from all new starts at 11,000 pharmacies during three different monthly periods. So we had three different curves that we showed you, amounting to several thousand patients, actually five or 6,000 patients at the beginning of each of those cohorts, and then followed those individual patients as long as they kept refilling their prescriptions.

That is, it was a sizable number repeated times three, nationally represented because then it was extrapolated from the 11,000 to the 35,000 retail pharmacies. We hold that it's a very good and stable and accurate measure and doesn't derive from one managed health care system.

So that as opposed to 16 percent in one year, our data is 40 percent of patients were persisting. We can argue about that one month bump at the beginning, and that has to do with how the first prescription was written and whether it crosses over. So their methodology is always to carry all of the patients from the first to the second month, but it does not affect the subsequent refilling over time.

So we can argue about this, but those data are very solid data.

DR. MARCUS: Your data were collected up through March of this year, and yours were through December?

DR. WATKINS: Through December, yes. We based our analysis --

DR. MARCUS: That's another three months that the number of people could have been on to pull out that --

DR. WATKINS: But the critical issue is

how many people are persisting at one year as opposed to whether you follow people along to say, well, how many go --

DR. MARCUS: I understand that, but I'm trying to reconcile these two numbers. It's conceivable with three months' more experience there could have been another 100,000 or so people who've been on it a year.

CHAIRMAN BONE: Let me see if I get -- one projection is 200,000. The other projection is 400,000. One projection is based on data from the HMO group.

DR. GRAHAM: Well, if I could explain though, that data comes from -- it's an IPA model plan, which means it's basically practitioners who contract with the plan to agree to that payment schedule, and it's over nine different states. I mean, it's not unrepresentative of the country.

CHAIRMAN BONE: I'm just trying to understand. One is based on this IPA group and the other is based on the pharmacy group, but whether it's 200,000 or 400,000, no body has seen a death attributed to the drug due to liver failure after patients has been on a year; is that right?

DR. GRAHAM: A case has not been reported.

CHAIRMAN BONE: Okay. That's --

DR. GRAHAM: That's different. That's different than saying it hasn't occurred.

(Laughter.)

CHAIRMAN BONE: Do I understand correctly though that no case reports are known to the company or the agency for patients who have been on the drug for more than a year?

PARTICIPANT: At this time.

(Laughter.)

CHAIRMAN BONE: Thank you, Doctor.

That's what I mean by known. That's what I'm trying to find out.

DR. GENUTH: Are you suggesting that if the patients just skipped the first year of therapy everything would be okay?

(Laughter.)

CHAIRMAN BONE: Thank you.

I knew having with this kind of experience would get us to a solution to the problem. No, I'm just trying to get one thing everybody agreed on. I enjoyed the moment.

(Laughter.)

CHAIRMAN BONE: Okay. Everybody here has got questions, and I'm sure several people, and we're

going to go around to the people who haven't asked questions yet and then come back.

Please, Dr. Hammes.

MR. HAMMES: Just a comment on that. The pharmacy data that the Parke-Davis folks are responding to, as a pharmacy professor and a pharmacist, I can comment on that.

Pharmacy students have been gathering that data since I was a student 30 years ago, and they actually go to community pharmacies and go through prescription files and record who got what and which companies was dispensed. It's quite accurate data.

CHAIRMAN BONE: All right. So we have two sets of accurate date. The question is how well we --

(Laughter.)

DR. GRAHAM: That is correct.

CHAIRMAN BONE: I think it's a question of how we extrapolate.

All right. Let's see. Dr. Fleischer.

DR. FLEISCHER: I would like to ask, again, just to the hepatologists who are here whether or not such an asyncratic reaction should be looked at in terms of person-time or person numbers. I mean, that's the next big discrepancy in the two ways to analyze the data, whether it needs to be done as

numbers of people versus the numbers of people over time.

And that really is the second large discrepancy between the FDA report from Dr. Graham and the company, and I wonder does anybody have any opinions about that.

CHAIRMAN BONE: Although we're trying to stick to the questions related to the Parke-Davis presentation --

DR. FLEISCHER: Oh, I'm sorry.

CHAIRMAN BONE: -- we'll permit this particular one because it --

DR. FLEISCHER: I didn't realize that.

CHAIRMAN BONE: Well, let's --

DR. FLEISCHER: We can wait on that.

CHAIRMAN BONE: We can finish it now and then come back. We've had the company's opinion and the FDA's opinion, and we'll ask the hepatologist's opinion, and then we'll be ready to go on with that.

DR. SEEFF: Well, since we're talking about an idiosyncratic reaction, we don't know precisely what causes it, and it could occur fairly early or could occur late. I think in general, at least in my experience, most cases if they have occurred have occurred within the first year. It's

been very rare to see severe hepatotoxicity occurring a year after one has begun this.

Now, the point that Dr. Graham makes is that this may be simply a question of the fact that there are very few people who are treated that long, and we may not have seen it, but I think the general consensus view and certainly among hepatologists is that if you're going to get your toxicity, it's going to occur within the first year. At least that's my sense of it. I don't know how Jim feels.

CHAIRMAN BONE: Anything thing to add, Dr. Lewis?

DR. LEWIS: Not really, but in answer to your question, I think it's a little bit of both. There are patients who are clearly on long-term drugs, different diseases. INH may stop at a year. Most of that injury is within the first two months to six months, but there are anti-convulsants and other things, and it's very unusual for us to see other idiosyncratic reactions occur beyond the first year of therapy.

I don't know how to interpret the fact that the number of events has actually gone down. If it's something idiosyncratic, it ought to be a constant rate per person, whatever that rare rate is,

unless the population has changed in some way.

There's going to be genetics involved here, and as Dr. Watkins pointed out, there's P-450 interactions and other things, and we don't know what predisposes individuals. You know, an unlucky individual gets this toxicity. We don't know what those factors are, but the monitoring should be able to reduce the number of severe reactions from early onset liver injury, and that's really what I would be focusing on.

Unless we're after a year when we don't expect to see any further injury, but up to that year, I guess if the numbers are falling off among newly prescribed individuals who are taking it out for more than six months, I'm not sure, you know, what's different about them that they're not getting the same injury.

I certainly understand it if somebody has been on it for nine months or a year. They're probably beyond the point where if they were going to develop a toxic metabolite or something, they're beyond that, and they're not going to get the toxicity, but I don't think the number should actually completely fall of detecting liver abnormalities.

But the monitoring will prevent the

fominant hepatitis.

CHAIRMAN BONE: Right. Okay. Just to close this point, I just want to ask a specific question, and I just want basically to know, and not a long discussion here. We either have data or we don't have data.

Do we know for a fact whether prescribing practices have changed with regard to initial prescribing in patients who might be judged at higher risk for hepatic problem by their doctor? In other words, are people being more careful about patients with alcohol histories or other reasons to be concerned about liver disease?

Does either the sponsor or the agency have actual data on that question?

DR. ZERBE: Well, we don't have data. I mean one would anticipate by the awareness and so forth it might decrease, but there are no data.

DR. GRAHAM: The only data we have are that the prescribing of troglitazone as monotherapy has increased in each of the three cohorts that we described.

CHAIRMAN BONE: But it doesn't address my question.

DR. GRAHAM: It doesn't? Well, we don't

have that data.

CHAIRMAN BONE: Thank you. That's what I'm trying to find out.

DR. GRAHAM: Well, unless monotherapy somehow or another was related.

CHAIRMAN BONE: Okay. All right. Let's see. Others. I don't think Dr. Illingworth has asked a question of the sponsor yet. Please do.

DR. ILLINGWORTH: I raised this this morning, but given the potential for drug interactions through the cytochrome P3A4 system, if you look at the patients who have had liver toxicity, has there been any link with co-administration of other drugs metabolized by that, or by a patient suddenly deciding, hey, I'm going to drink three glasses of grapefruit juice a day? Does that influence it?

DR. ZERBE: Paul, I think you're the best.

DR. WATKINS: There have been a couple of patients who were admitted to the hospital and then clearly had a great acceleration in the rate of liver injury in very confusing settings with fevers, antibiotics, et cetera.

And actually that was the first time, and this is an area of my expertise, I thought of the possibility that induction of 3A4 perhaps with a

certain antibiotic or something might explain that, and it was a very perceptive point.

But there is no data that I'm aware of, and I'll go back now and take a look to see if something like that may make some sense.

And your second question? Oh, the grapefruit juice. Yeah, grapefruit juice only affects 3A4 in the intestine, which should be irrelevant to the issues we're talking about here, I think, unless you have more insight than I do.

DR. ILLINGWORTH: I don't know. Is the drug metabolized in part by the CYP 3A4 in the intestine? Is less going to go to the liver because it's metabolized at the intestinal level?

DR. WATKINS: Yes, it's a very good point. I don't know the answer to that. It's a good thought.

CHAIRMAN BONE: Thank you, Dr. Illingworth.

Are there any other members of the Committee who have not asked a question yet of the sponsor?

Dr. Hirsch, please.

DR. HIRSCH: I don't know. The sponsor might know this, and I'm just wondering about as of this moment the current prescribing practice. That

is, I'm assuming that there's two reasons for using the drug. One is that it might be better than other drugs for monotherapy, let's say, or useful as an adjunct to other drugs when the others are failing.

So I guess the question is in both sides. Let's take the failing side. What fraction of people on sulfonylurea, insulin, et cetera, are failing and now are getting Rezulin as compared with the total group who are succeeding?

DR. ZERBE: Well, I think, if I can make the question simple, perhaps a proportion of patients that are on monotherapy versus combination, we just followed up on the comment made by Dr. Graham. We don't agree that there's been a change in the frequency of monotherapy prescribing. That, in fact, has remained stable. This is worldwide -- well, not worldwide data but, you know, nationwide data, not within the specific health care system that Dr. Graham looked at.

So it's actually been very stable over that period of time, and as I recall, the number is around 20 percent monotherapy; is that right?

DR. HIRSCH: Twenty percent of monotherapy is Rezulin; is that --

DR. ZERBE: No, no, no. I'm sorry. Was

that the question? I thought the question was --

DR. HIRSCH: Well, that's one question.

DR. ZERBE: -- whether there's a difference between monotherapy and combination.

DR. HIRSCH: In monotherapy, how much Rezulin is used, and how much Rezulin is used not in initial monotherapy?

MR. WITCHER: I'm Jay Wright Witcher.

In the entire market, Rezulin monotherapy accounts for not more than approximately two percent of prescriptions. The breakdown of usage of Rezulin is approximately in the period October to December 1998, for example, 20 percent monotherapy and 80 percent combination with one or more other drugs.

That percentage as a percentage of total has actually declined from early 1998 when monotherapy accounted during the first quarter of 1998 for as much as 28 percent of use.

DR. HIRSCH: No, I've got two percent as monotherapy. Tell me now the percent of people who are on multiple drugs who are getting Rezulin

MR. WITCHER: The percent of the total or the percent of Rezulin?

DR. HIRSCH: All people who are getting sulfonylurea, insulin, metformin, whatever, who also

are -- what fraction of those fail and now get Rezulin?

MR. WITCHER: That's a somewhat different question.

DR. HIRSCH: Yes, it is.

(Laughter.)

MR. WITCHER: Toughly in the market right now, the total amount of -- you sort of want to know what's the total amount of monotherapy versus combination therapy.

DR. HIRSCH: No, no. You've told me that two percent of people on monotherapy are getting Rezulin; is that correct?

MR. WITCHER: That's correct.

DR. HIRSCH: Okay. Period.

MR. WITCHER: Yes.

DR. HIRSCH: Now, people on other therapies --

MR. WITCHER: Yes.

DR. HIRSCH: -- all of these other drugs, what fraction of them fail and get Rezulin or something of that sort?

Do you see what I mean?

PARTICIPANT: How many people are getting combination therapy with --

DR. HIRSCH: With Rezulin versus those who get combination therapy without Rezulin.

MR. WITCHER: Combination therapy with Rezulin right now is approximately 80 percent of Rezulin usage. I think I'm missing the point.

CHAIRMAN BONE: Dr. Hirsch is asking the question of all patients getting combination therapy, in what percentage is Rezulin being used.

DR. HIRSCH: Is Rezulin one of the combo.

MR. WITCHER: Of all patients, that would be probably -- of all patients getting combination therapy, which is roughly 27 percent right now of everybody, something like perhaps 20 or 30 percent of those would be getting Rezulin right now.

DR. HIRSCH: Okay. So 20 or 30 percent of those.

MR. WITCHER: Right.

DR. HIRSCH: I've got it. Thank you.

CHAIRMAN BONE: And that would be about five percent of all diabetics then or something like that?

MR. WITCHER: Yes.

CHAIRMAN BONE: Thank you.

DR. HIRSCH: Good.

CHAIRMAN BONE: Okay. We got one. Okay.

Dr. Hammes.

MR. HAMMES: One key question comes to my mind, and I'm not a diabetes expert by any means. I'm a nuclear pharmacist. Dr. Graham's data on the population based risk basically hinges on two cases; is that correct? Two in your studies.

DR. GRAHAM: I mean, I think if you're talking about the DPP trial --

MR. HAMMES: The DPP and the REACH.

DR. GRAHAM: -- and the REACH trial.

MR. HAMMES: yes.

DR. GRAHAM: I think -- I don't think it just hinges on that. I think that -- but you're entitled to draw your own conclusions.

MR. HAMMES: Your incidence rate I'm looking at.

DR. GRAHAM: Well, right.

MR. HAMMES: You have two deaths basically.

DR. GRAHAM: We have those population based studies, and then we have our life table modeling.

MR. HAMMES: Okay.

DR. GRAHAM: And that gives us a very similar rate to that found in the DPP and in the

REACH.

MR. HAMMES: And now we heard data from the sponsor that suggested that both of these cases were confounding diseases or etiologies that could explain at least a significant component of the liver failure. I really need that expounded on.

If the risk from this side hinges on two people, and both of those could be explained by a different cause, I think that needs to be looked at a little harder here.

CHAIRMAN BONE: Well, I guess have the medical officer of the FDA and the physicians from the sponsor met on those specific patients?

DR. GRAHAM: We have, and the company has classified both of those as probable cases of acute liver failure with troglitazone, and that was on their slide.

CHAIRMAN BONE: Right. Now --

DR. ZERBE: Well, I think to say it's probable and to say it's absolute, of course, are two different things. We, in fact, have conceded the points. There are complicating factors. We are not trying to explain away any cases.

I think the other important point or perhaps even more important point to discuss with

regard to the population estimates or the methodology are really selecting trial and not looking at the whole database.

If you look at the confidence intervals that are created when you look at the whole database, those confidence intervals actually do encompass our estimates of baseline spontaneous reports. I think that is the more issue than to try to discount the cases.

There are many complicating factors on it, but we're not trying to walk away from the responsibility in those cases.

CHAIRMAN BONE: I think that leaves that question partially answered.

Dr. Temple wishes to make a remark.

DR. TEMPLE: There's been some discussion about the difference in methodology used to address the population based material, and there's one crucial point. Dr. Faich explained why he thinks you should count each patient once whether they're on it for a week or a month or a year, and David, of course, did it differently. He did it per patient-year.

When you use the same method, I suspect you get numbers that are not terribly different because you only had 5,000 patients. So if the number

changes by 30 percent, it won't change that much, but I had a question for Dr. Faich.

There's a continuing risk for at least six months that looks very much the same. It's not one of these things where all of the risk is in the first week. So don't you feel at least -- or month -- don't you feel at least some obligation to discount patients who are only on treatment for a very short time?

Maybe you don't like David's approach to do it per patient-year, but you've got to do something for people who are treated only briefly.

DR. FAICH: Well, on the one hand, if we do that, then we have to throw out the cases that occurred in the first month of therapy from the numerator to some extent if we're going to do this, but, on the other hand, this is where this persistence issue becomes very important.

It is true that some 20 percent of starters don't have a second prescription, depending which data you look at.

DR. TEMPLE: I just need the population data. You have the duration of therapy in all those cases. I mean just the population cases.

DR. FAICH: So what you're saying is if you get rid of, adjust the denominator, take out those

patients who discontinue early because they're not at risk. Is that right?

DR. TEMPLE: No -- yes, that their risk may be --

DR. FAICH: In which case, you're going to remove ten percent or 20 percent of the total number of new starters. I'm suggesting it's not that large. In some areas, in some drug classes, it becomes very important because 80 percent of patients never fill the second prescription, but that doesn't appear to be the case here.

DR. TEMPLE: But you actually have data here. So you can do it. The point is there seems to be a continuing risk or more or less constant risk you could actually say at least for six or eight months. You just counted patients as one whether they were in for a month or for eight or nine months. That's not what epidemiologists usually do, but you can argue those points.

But you might have done it zero to three months, three to six months. There's a lot of ways to do it, but you only just said one exposure is an exposure.

DR. FAICH: The issue here is whether your monthly risk changes over time. You're just saying

it's constant over time, but if we're going to sum -- what I'm saying is something different. I'm saying that you have that monthly risk in month two, month three, month four, month five. It's constant, but that, in fact, if you're susceptible -- it's an issue of susceptible -- you're only susceptible once. You're only going to get it once.

So that you don't have to actually sum person times. You sum the number of people who stayed in for more than -- I'm willing to acquiesce to saying, you know, you have minimal risk in the first month.

CHAIRMAN BONE: Thank you.

Okay. I think the Committee are intelligent enough to figure out which they think is appropriate here.

I think we have several questions left. These are all questions pertinent to the sponsor presentation; is that right, from the Committee? Dr. Illingworth just asked a question. Dr. Molitch, did you have a question for the sponsor?

DR. MOLITCH: Yes.

CHAIRMAN BONE: Go ahead.

DR. MOLITCH: Do we have a breakdown on the kinds of physicians who are prescribing Rezulin

because this may have something to do with the ascertainment of cases?

DR. ZERBE: I'm sure that's something we do have, but I don't have it at my fingertips, but can we go on with the next question?

DR. MOLITCH: Sure.

DR. ZERBE: And we'll come back with the answer just to be --

CHAIRMAN BONE: Dr. Cara had a question.

DR. CARA: If you don't think that there is continued risk with continued exposure, then what is the value of continued monitoring?

DR. ZERBE: Well, there are changes in the -- there are changes in the recommendations for the frequency of monitoring after eight months. So there is some decrease. I think we have just been reluctant to totally eliminate monitoring. We don't know yet whether there will be cases at a later point.

I think that, you know, the idea that there will be none is probably unrealistic. At some point there will be cases later on. They may or may not be related to the drug, but they will be reported, and I think that's a realistic expectation.

DR. CARA: If you look at that graph that we've talked about a couple of times now that's on

page 19 of Dr. Pierce's presentation, what's a little bit disturbing to me is if you look towards the tail end of that, you know, 18 to 19 months, there's a blip up that's fairly substantial.

Now, granted those are few patients, but if we're indeed talking about a few patients and the jaundice/hyperbilirubinemia rate per 100,000 patients is actually going up at that point --

DR. ZERBE: I think I can answer the question. If not, I'll call up the colleagues, but we obviously have looked very carefully at that.

Dr. Pierce pointed out that that basically is essentially one patient at each of those months, and the reason it appears to be going up is the denominator, the numbers of patients exposed at that very extreme end of the curve, is going down so dramatically.

So the problem is, you know, it's unstable data at that point, frankly, and bilirubin and jaundice, of course, is even more difficult to assess in terms of specific etiology.

CHAIRMAN BONE: Thank you.

Are there other questions? Dr. Illingworth and then Dr. Genuth.

DR. ILLINGWORTH: Recognizing the sort of

ethical issues concerning rechallenge, have any patients you've had a rise in liver enzymes then gone back down after the drug has been stopped been re-given the drug to see whether they re-get a rise in liver enzymes?

DR. ZERBE: Well, in terms of a rechallenge, you mean? I believe there have been some, but perhaps the more important issue, and I think Dr. Whitcomb mentioned it or somebody mentioned it -- it may have been Paul -- in the clinical trials there were patients that had elevations, as you'll recall, and 50 percent of those patients -- this was, you know, up to the discretion of the physician whether they stopped the drug -- 50 percent of the patients continued therapy and returned to normal while on drug.

Now, we're not suggesting that be done obviously, but it does point out that, in fact, you know, it's not irreversible in all situations. Unfortunately, we can't tell which ones they are. So they all have to stop.

CHAIRMAN BONE: I'd also raise the possibility that they might have had some other reason for enzyme elevation besides what's going on here.

DR. ZERBE: Yeah, and I think that's a

very important point, particularly at the level of enzyme elevations that many of them, you know, were describing.

CHAIRMAN BONE: Yeah. I mean, we always see some changes in liver enzymes during clinical trials which may or may not be related to the test drug. So we may be talking about two different or more than two different reasons for enzyme changes.

Was that the point you were getting at here?

DR. GRAHAM: No. We have -- one of our cases of acute liver failure was a patient who developed hepatitis, had an ALT that rose up to, I believe, around 700, was stopped on the drug, and then a couple of weeks later was restarted. We don't know what their ALT was when it was restarted, but then that patient over the next six weeks went into liver failure.

DR. ZERBE: Just so that, you know, there's full disclosure of information, I have been told that we have rechallenged six patients. Three did return, go up. I don't know whether this case was amongst them or not. This was in clinical trials, and three went up and three did not go up on rechallenge.

CHAIRMAN BONE: I take it you're not

planning to do that again.

DR. ZERBE: No.

CHAIRMAN BONE: Thank you.

Dr. Marcus.

DR. MARCUS: I see from those of us with airplane schedules that the two-minute warning has sounded. I have a suggestion to make that I think may be helpful to the sponsor, and I want to make sure that it gets here before we have to disband early.

It's clear from what I've heard that it seems that the source of the reporting for jaundice and liver problems is coming not from physicians so much as it's patient driven.

Furthermore, I've heard from our hepatologist colleagues that the rate at which ALT goes up can be very precipitous, indeed, and so the question is whether a month, even once a month screening is adequate is questionable.

Now, if the patient has to come into the doctor's office once a month, that's a little bit of a burden. If you're asking them to come in once a week, that's even more of a burden and probably impractical.

But the one thing we do know about diabetics, is that they are willing to do daily home

glucose monitoring, and there are methods for doing home monitoring of all sorts of things on just a drop of blood.

You could ask for the first year of therapy, could you not, that a patient monitor his ALT once a week or even on a daily basis and try to pick up these things when it is in a very early stage. I could see that even with the same drop of blood, if you had some clever device company that Dr. Sobel could push through approval for --

(Laughter.)

DR. MARCUS: -- you could get a simultaneous readout of a blood glucose and an ALT, and that could solve a lot of this problem of screening.

CHAIRMAN BONE: All right. I think that's an interesting way to look at this in the future.

I think if we've completed asking our questions -- oh, no, Dr. Genuth. I'm sorry.

DR. GENUTH: I think the gentleman who is going to cure liver disease with a device might be interested you idea.

(Laughter.)

DR. GENUTH: Some member of the sponsor's team -- I can't remember which -- emphasized the word

"persistence," I think in connection with the fact that at the end of one year of Rezulin, there was still 40 percent of the people still taking it. Now, maybe this is the cup is half full, the cup is half empty problem, but I would look at that and say at the end of one year 60 percent of the people who started on Rezulin are no longer taking it, and I'm wondering why.

Now, it's not because of jaundice or hepatic failure. I think no matter what the debate is on the incidence, it's not 60 percent. It's not likely to be side effects because in the clinical trials all the usual kinds of complaints of patients are not any higher than in the placebo group.

It might be lack of efficacy, that is, the physician has tried it and has given up, and it could be price, and I know this isn't exactly the place to get into economics, but some of my patients tell me that is a problem.

Do you have any idea? I mean how good is a drug that's going to have to be given for life if after one year 60 percent of the people aren't on it anymore?

MR. WITCHER: Well, unfortunately, the first part of the response to that question is that

this data, which is broadly applicable to any chronic care therapy and is used as an industry standard, is not dissimilar for chronic use of virtually most any drug you can think of, Dr. Genuth, whether non-steroidals or, you know, statins or other drugs like that.

It is commonly the rule that in chronic care 50 percent of patients are off drug after six months, and we have -- the second part of the answer to the question is we have looked retrospectively using market research techniques to go back and ask about reasons for discontinuation, and you touched on them, and they're all over the map.

Patient lost to follow up, switched to another agent, does show up. Cost influences it. It's all over the map, and there's no particular pattern that emerges.

CHAIRMAN BONE: What happens on your database if somebody just changes pharmacies?

MR. WITCHER: That is also similar for other diabetes therapies. Excuse me. Pardon me.

CHAIRMAN BONE: What happens if they just change pharmacies?

MR. WITCHER: That's a phenomenon that causes a dropout in the way the data is collected, and

we've worked extensively with the people who collect this data, and they feel very confident that the data is nonetheless broadly applicable.

CHAIRMAN BONE: Obviously that consideration would not apply except in people changing their health plans. Then I guess you'd have the same loss.

DR. GRAHAM: Right. I wanted to make a comment about why the difference in their persistence curve and our persistence curve, and I think it has to do with what we've measured and how we've measured it.

We took a cross-sectional snapshot of everybody within a captured population who ever took troglitazone, and that includes people -- a person who just started troglitazone, say, in November of '98 in our cross-sectional snapshot would show up as somebody who's only on the drug for one month.

What the company has done is they've taken sort of like three different periods of time and followed a cohort of 100 people or 1,000 people out as far as they can to see what the actual pattern of use is in those people.

But if you were to take those three things and superimpose them now to say, well, what does the overall shape of the curve look like, it would end up

looking like our curve.

CHAIRMAN BONE: Are you telling me that when you're saying that 16 percent of the people are remaining on drug after a year --

DR. GRAHAM: No. What that 16 percent says is that for the time the troglitazone has been on the market, 16 percent of people who ever used troglitazone, and that includes the people who just started it in December; those people, that 16 percent of all those people are still on it a year.

Now, if we were to break it down by cohorts, cohort one, cohort two, cohort three, well, the people who are contributing to the long time at the end are people who started in cohort one, because they had the opportunity to be on the drug that long.

CHAIRMAN BONE: I think the Committee understood you to be saying that people who started the drug a year ago, only 16 percent were remaining.

DR. GRAHAM: No, no, no. This was cross-sectional data, and the importance of it is when you want to model what is the distribution of total prescription use in the country, that you have to do it that way. You can't look at the model the way they have because it will overestimate what the total burden in the population is.

DR. HIRSCH: What percent do remain? I can't figure this out.

CHAIRMAN BONE: Do I understand then -- I think what you have to do or what you don't have to do might depend on what you're trying to analyze, but do I understand then that Dr. Graham would not dispute the sponsor's estimate that of people who started the drug a year ago, 40 percent may remain on therapy at the present time? Does that sound like we're not disagreeing about that?

DR. GRAHAM: We haven't addressed that question and analyzed it. So we're not in a position to say whether we agree or disagree. We looked at something very different because we wanted to model all prescription use in the country. We wanted to model time, exposure time and risk.

CHAIRMAN BONE: Okay. So you're looking at a different point there altogether. I think that's very important for everybody to understand. It wasn't clear to me until just now.

Thank you.

Dr. Seeff.

DR. SEEFF: You sigh as you say that.

I'm very intrigued with a comment that was made earlier about the frequency of monitoring. I

think that all of us will agree, and I think that Dr. Watkins will agree that the ALT is not the best way to monitor. It's the best thing that we have. We really don't know how to monitor for hepatotoxicity and much more research needs to be done, and I can tell you that NIDDK is thinking very seriously about this issue and wants to proceed by looking for a better way of monitoring for hepatotoxicity not only in people who have normal enzymes, but in people who have abnormal enzymes and who's put onto a drug.

I do think that the figure of three times the upper limit of normal is a rather arbitrary number, and while I think that the sponsor has done a great job with the hepatologists of trying to work out when to test, that is, if it goes up to more than one and a half times the upper limit of normal, call the patient back a week later, test, and then when you get to three times the upper limit of normal withdraw; I'm not sure that that should be done.

I think it maybe should be more sensitive, and if it goes up a second time, I would already begin to be very concerned, but I think that this is an unusual opportunity if everything works out otherwise to, in fact, do a study to look at this in people who are, in fact, having blood drawn on a regular basis

and learning more about what happens and looking for other means of determining hepatotoxicity.

CHAIRMAN BONE: Thank you, Dr. Seeff.

Are there any further questions directed at the sponsor?

(No response.)

CHAIRMAN BONE: All right. Thank you.

All right. It's now 4:18. I think that we will clearly dispense with the intermission that was originally planned for the afternoon and ask everyone's endurance here.

I'm sorry.

(Pause in proceedings.)

CHAIRMAN BONE: Thank you.

The next item will be the summary and charge to the Committee and introduction to the questions by Dr. Bilstad, followed by some discussion within the Committee, and then we'll address the questions.

Dr. Bilstad.

DR. BILSTAD: Henry, I wonder if we could have just a moment to answer some points that were made about the United Health Care Study, some comments that were made by Dr. Pierce?

I would like Dr. Graham just to --

CHAIRMAN BONE: Very briefly, please.

DR. BILSTAD: -- address just a couple of issues that I think are important for understanding.

CHAIRMAN BONE: All right if you're sure that the Committee didn't understand it before.

Thank you.

DR. GRAHAM: Right. Regarding the UHC data that we used for our enzyme monitoring study, Dr. Spurgeon is not the Chief Medical Officer for the United Health Care as stated by the company. He is the Medical Director of one of the UHC affiliated health plans of which there are 13.

Now, the question Dr. Spurgeon raised in his letter to Parke-Davis was shared by Parke-Davis with us, and we immediately investigated the questions that were raised in Dr. Spurgeon's letter.

After doing that, we communicated our findings to the company yesterday. It turns out that Dr. Spurgeon was talking about a small and not well documented survey that he and others in his plan conducted in a group of people in a rural setting. The problem he identified was not found in metropolitan areas, which accounts for most of the UHC database.

Also, Dr. Spurgeon's health plan relies on

capitated data, which is known to be of low quality because of incompleteness.

For this reason, the Research Center for United Health Care does not use data from Dr. Spurgeon's capitated plan in their research database, and the problems he raised are not applicable to our study.

I also spoke with the real Director of Research for United Health Care, and she is confident that the problems described do not impact on our data.

CHAIRMAN BONE: Thank you.

As I said -- thank you very much, Dr. Graham -- as I said, we'll now ask Dr. Bilstad to give his summary and charge to the Committee and introduction to the questions. We'll have a period of time for the Committee to discuss further amongst ourselves, and then we'll address the questions concerning which the FDA has asked our advice.

DR. BILSTAD: I'm going to speak from here, Henry.

CHAIRMAN BONE: Fine.

DR. BILSTAD: And my comments will be very brief.

CHAIRMAN BONE: Thank you.

DR. BILSTAD: Lanh, could you show the

first projection?

Obviously assessing the benefits and the risks in this situation posed a significant challenge for all of us, and we've heard data from Dr. Graham on the risk side that we feel is cause for concern. The sponsor has presented information about the short-term and potential long-term benefits of troglitazone.

Could I have the next one?

Certainly lowering blood sugar is well accepted as an important goal in the treatment of diabetes, and support for the effect of better control for hyperglycemia comes particularly from the DCT and from the U.K. PDS, and the data mostly support the effect on microvascular complications.

The next slide.

The problem really is how directly we can extrapolate from these data to troglitazone, which of course has not been studied long term.

I did want to just briefly, if you could go -- yes, I wanted to mention some of the regulatory options that are available in this situation, and this is by no means meant to be comprehensive or exhaustive.

The first option: continue to monitor closely the number of reported cases of liver failure.

Basically that would be the watchful, waiting approach. That could be combined with increased educational efforts and other efforts.

The second option listed is to decrease the recommended time interval for monitoring liver function, and that is if you believe that decreasing that interval would help to pick up some additional cases. It raises the question how many cases it would pick up. Obviously there becomes a point of diminishing returns. That comes at a great cost, too.

The third option I have listed is to make the distribution of the drug dependent on monitoring liver function, and this can be done under what we refer to as Subpart H of the regulations, the so-called accelerated approval regulations, a part of which deals with restricted distribution if that is necessary from a safety standpoint to be able to use the drug safely. So that is an option if it was felt that monitoring is very essential to preventing cases of severe liver failure, and if, in fact, we were convinced that monitoring really was not being done even in the face of labeling recommendations and educational efforts.

Next slide.

And finally, another regulatory option

would be, of course, to eliminate one or more of the indications based on the assessment of benefits and risks, and one of the ones certainly that has been questioned, whether the benefits do outweigh the risk, is in the case of monotherapy.

So with that, I will close. Obviously there's a number of areas here where we don't have all the information, but we're asking the Committee to try to answer the questions based on the information that we have available at this time.

Thank you.

CHAIRMAN BONE: Thank you, Dr. Bilstad.

I think what I'd like to do now -- did you have any further comments on the questions at all?

DR. BILSTAD: No, I was going to leave those to you. I have them on the projector if anybody -- but I don't think it's necessary. Everybody has them.

CHAIRMAN BONE: Yeah, and I think the audience all have copies, as well, if I'm not mistaken.

All right. Well, everyone is familiar with the question. I'm just going to give a quick overview, go back to the Commission discussion, and we can come back to the questions.

The first question has to do with whether the benefits of this therapy outweigh the risk for each of its approved indications.

The second question has to do with if the answer to the first question is yes, how can that be improved.

And the third question, if the answer to the first question about the favorable benefit-risk ratio is no, how could it be modified or improved by a change in the labeling.

And the fourth question has to do with comments about the use in combination with both sulfonylurea and metformin.

And the fifth question has to do with what additional information should be sought.

I'm just going to go around, I think, in as systematic a way as any, to just go around the table and invite comments from each of the members of the Committee. This may generate some discussion.

We're hoping to be able to conclude at a reasonable hour, but the most important thing is to adequately discuss this very serious issue. So we want to make sure that we have done that, that important points are all given adequate consideration.

Perhaps I'll just start with Dr. Hirsch

and work around the table.

DR. HIRSCH: Well, I'm going to base my answers to the questions on the way I understand what happened today.

CHAIRMAN BONE: Okay.

DR. HIRSCH: And my own understanding of this, and I'll be very brief.

CHAIRMAN BONE: I'm not asking you to answer the questions now.

DR. HIRSCH: I'm not going to answer the questions, sir.

CHAIRMAN BONE: Okay.

DR. HIRSCH: I'm just going to give you the facts on which I'm going to answer the questions.

CHAIRMAN BONE: Okay.

DR. HIRSCH: As I understand them.

CHAIRMAN BONE: Very good. That's just what --

DR. HIRSCH: And I hope everyone will do something like that because that might help us.

I have now some estimate in my own mind of the confidence limits of this problem, and I think that in five years either there will be hundreds of people who will have died of liver disease or thousands of people, and it's not clear, and I don't

think I know how to make that evaluation, but I think it's somewhere in that range.

I think that the business of trying to determine by ALT or other available techniques who's going to get that is a weak read at best, but it is prudent, I think, to keep following this sort of thing in my own kind of mind.

Now, I'm going to base my judgments on the following. Given the fact that there is this risk, which I believe has some tangible element to it, I now want to apply this drug to where it does definitely most good, and that is in the case where other known drugs have been tried and are failing, and this may prop up the patient and make a better situation vis-a-vis the complications.

There was no time to attend the many other matters, like the inevitable weight gain that does seem to go on in most of the studies, and I note that that's not factored in. That is, weight loss modifies Type 2 diabetes. Weight gain makes it worse, et cetera.

But even so, I do believe that troglitazone improves the lot of people who are on other drugs and are failing, and I think it should be used for that and that only.

CHAIRMAN BONE: Thank you.

Ms. Killion.

MS. KILLION: Well, I think there are some serious -- well, I think we know that there are serious areas of concern here. The four that I seem to respond to from my perspective was that there seemed to be fundamental disagreement about whether the treatment, the use of the drug, whether there's a window of risk that you pass through at a certain time and then you're safe or safer, or whether there is a cumulative risk, that the longer you're exposed, the greater your risk of developing something, that you don't pass through safely at some time.

Then there seemed to be an idea of patients, which of course I'm concerned about whether there is in the patient population a certain percentage of people who are susceptible to this liver problem and, therefore, their exposure to the drug, which unfortunately we can't identify these people yet, is a problem, is a serious problem, or whether there is, again, this idea of cumulative risk where even if you were not susceptible, even if you're just otherwise functioning, your continued exposure may create a susceptibility that was not genetic or some otherwise in place at the time.

So those are the areas that I thought, and when I'm considering this as a patient, as someone with diabetes, I have to respond to a comment that was made earlier at the meeting that seared me, which was that patients don't care whether they die of a troglitazone reaction or diabetes.

That is not the case. You know, the advances that have been made in diabetes over the last ten years are phenomenal. I'd like to be around for as many of those years as possible. Maybe we'll find a cure for this problem, but the treatment certainly -- I don't want the treatment to be worse than the disease.

And so it is important. We do want something that works that has an efficacy value to it, and we want our risks reduced. So limiting it to certain people, if we can identify, that is the way we need to go.

CHAIRMAN BONE: Thank you.

Next is Dr. Fleischer.

DR. FLEISCHER: Well, I think that the drug has excellent effect in diabetes management, but I think the issue is which of the models for the liver abnormalities are going to be correct, and so prudent continued monitoring and following of this in some

accurate way is critical to what should happen.

CHAIRMAN BONE: Thank you.

Dr. Colley, do you have comments?

DR. COLLEY: I would echo that. I don't think the story is completely known yet based on the huge discrepancy in the numbers of patients believed to be at risk for liver failure. For that reason, limiting exposure and increasing the adherence to the monitoring would be critical, in addition to educating patients.

A lot of the symptoms that may occur are very nonspecific and may not otherwise cause concern, and before a patient takes this drug, they need to be very aware of what type of symptom they should be bringing to their provider's attention.

CHAIRMAN BONE: Thank you.

Dr. Cara, do you have comments you want to make about the general discussion here?

DR. CARA: I've tried to sort of summarize in my own mind what I've learned or at least make some conclusions, try to reach some conclusions about the information that's been presented today, and what I've sort of thought about for my own based on what I've heard is that I think the incidence of liver disease is significant, but the mortality is relatively low

when you look at it in the context of everything that can essentially hurt or kill a person with diabetes.

And in my best estimate from what I've heard, I'm sort of guessing at an average mortality rate of about one to 5,000 with metformin from liver disease.

The other conclusion is that monitoring has a place in reducing mortality, but it may not be carried out as indicated necessarily by physicians. So that I think that full disclosure and patient awareness is especially critical.

I think the benefits are very clear, especially when used in combination with insulin mimetic or insulin treatment, insulin medications, such as sulfonylureas, perhaps metformin, and with insulin because of the fact that a glycohemoglobin drop of one and a half to two units is very -- has very significant impact on overall mortality and morbidity related to diabetes.

There's still the issue of weight gain, and that really needs to be adequately addressed and effectively treated.

Those are the conclusions that I've reached, and I would propose that Question 1 be modified a little bit based on the questions that

followed to sort of cross off the part that says "with the currently labeled indications, warning, and precautions," and then talk about those in two and three.

CHAIRMAN BONE: Dr. Kreisberg, please.

DR. KREISBERG: Well, it's very apparent that reasonable people can disagree, and we've heard from noted experts today about what they think the risk is, and I find it incredible that there's so much divergence in opinion.

I think this is an important new class of drug, and I'm going to rely very heavily on valued colleagues who practice and take care of patients with diabetes on a day in and day out basis and see lots of them.

And I've read through all of the letters of testimony, as well as hearing the testimony today, and to a large extent, I think this information is as valuable or more valuable than the theoretic issues that have been brought up here that are based on modeling and very few events.

CHAIRMAN BONE: Thank you, Dr. Kreisberg.

Dr. Molitch.

DR. MOLITCH: I don't think I really have much to add, though much has been said already. I do