inconclusive and conflicting. I don't think this is by design.

Let me take this second point first, the lack of rigorously collected data, and say when these drugs are being developed there's very rarely, if ever, an a priori suspicion that the drug might cause depression. So, it's not rigorously looked for. Usually this comes up postmarketing, and they're picked up as case reports by clinicians, as we've heard Dr. Byrne, just previous to my talk, noticed some cases in which he thought there might be an association.

When trials are done, they tend to be retrospective and observational rather than prospective, randomized and controlled, which are the type that are generally relied upon to make more definitive statements about causal links. Case reports again might be considered a signal-generating mechanism.

Studies that are done rarely employ established observer-based rating scales. I'd like to contrast that with the lack of any rating scale with spontaneous reports might be used in some studies. As opposed to observer-based, they're self-report scales. An example of that is the Beck Depression Inventory, which was used in one of the studies mentioned earlier this morning.

Self-report instruments are usually regarded as

sensitive and certainly easy to use and user-friendly, but they're not regarded as being that specific and can give some false positives which can be good and it can be bad. The low specificity can give you a high rate of noise, which can be confusing. The false negatives can just obscure any possible signal-to-noise ratio.

Here's a list of drugs implicated in depression. I want to emphasize the word "implicated." I don't think any of these have been proven to cause depression for the reasons that I mentioned before. These were picked up postmarketing again and the lack of rigorous studies. Several of these surface again in the literature, but as you dig into the literature, you'll frequently find that they ultimately rest upon case reports and you'll find even different conclusions on that, I believe as Dr. Jacobs mentioned, even for beta-blockers which are on the list here. None of these are rock-solid. There are reports on either side.

Corticosteroids, ACTH, sedative-hypnotics, alcohol, L-dopa, anticancer drugs, oral contraceptives, the antihypertensives mentioned before, and reserpine, which is no longer on the market, but it's the observation of association between reserpine and depression. Whether it was real or not is another matter. But the observation of a possible association led to the implication of

norepinephrine in depression and subsequently led to further research into the possible role of norepinephrine in depression. Now we know that even some of our older antidepressants, such as desipramine, act on norepinephrine, desipramine being a potent norepinephrine reuptake inhibitor.

So, not is all bad when we see an association between drug and some adverse event. In the case of depression, it might lead to further research and might clue us into the pathophysiology of it and how it might be treated.

And interferon is last on the list.

This is my next-to-the-last slide, although it says "summary." So, many drugs with various mechanisms, such as those shown on the last slide, have been implicated. In theory any drug that can cross the blood-brain barrier and bind brain receptors can affect the brain, can possibly in theory.

However, there are few rigorous studies of drug-induced depression. So, anything is possible but it's another matter to really rule something in or rule something out.

There's a lack of consensus on causality and the scope of the problem, the problem being drug-induced depression again.

This is my last slide. So, depression is common but under-recognized, making it difficult to make definitive statements based upon any signals we might see.

Depression may be especially under-recognized in adolescents.

Suicide is a leading cause of death, especially among adolescents. Again, it was number three.

And the spontaneous reporting system or the Adverse Event Reporting System, or AERS, referred to earlier, underestimates the number of adolescents with drug-induced depression for various reasons. We know so little about drug-induced depression. Adolescents might be especially under-reported and depression in general is certainly under-reported as well.

And that's it. Thank you.

DR. BERGFELD: Thank you.

The next presentation is that of the case review by Dr. Marilyn Pitts.

DR. PITTS: Thank you. Madam Chair, Dr. Woodcock, committee members and guests, good morning. My name is Marilyn Pitts. I'm a safety evaluator in the Office of Postmarketing Drug Risk Assessment.

My objective today is to describe the positive dechallenge/rechallenge cases of Accutane associated depression, depressive symptoms, and mood disorders.

The top 10 adverse events for Accutane include depression, ranked number 6. By contrast, we looked at tetracycline, which is another agent used for less severe acne. We have 8 cases of depression and 2 deaths, and we looked at Claritin in the AERS database where we have 10 cases of depression and 2 deaths.

In evaluating spontaneous adverse events, positive dechallenge/rechallenge cases provide the best evidence to support a relationship between a drug and an observed event.

Today I will discuss the FDA's principal data source for detecting rare drug adverse events. I will provide reasons for suspecting a drug/adverse event relationship. I will describe the dechallenge/rechallenge cases included in the 1998 case analysis, as well as cases included in the year 2000 analysis. I will also present a case summary for the 1988 and the year 2000 case series.

The FDA's Adverse Event Reporting System, or AERS, is a computerized database of adverse events reports. The database is searchable by drug names and key words. The database was established in 1969 and updated in 1997. Individual records within the database are based on submitted MedWatch forms.

MedWatch forms are voluntarily submitted by pharmacists, physicians, nurses, and other health care

professionals and consumers. Approximately 94 percent are submitted directly to the manufacturer, and the remaining amount are submitted directly to the FDA. The manufacturer is required to submit all MedWatch forms to the FDA. Serious unlabeled events are expedited and submitted to the FDA within 15 days. All other events ar submitted on a periodic basis.

The strengths of the adverse event reporting system is that the system is simple. The system is sensitive. A small number of cases can lead to the detection of a signal. The system is good for detecting rare and unusual events, such as hepatic failure or aplastic anemia. And the system is relatively inexpensive when you compare it to alternative surveillance strategies.

However, there are limitations. One limitation is that incomplete data is submitted. On the data form, there are many fields missing. For example, race is not encoded. When reported, race is usually reported in the narrative. In addition, even coded information can be missing. The narrative information can vary in quality and in quantity of the documentation submitted.

Another limitation is under-reporting, which is substantial. The FDA receives notification of only a fraction of adverse events. The amount of under-reporting cannot be quantified or predicted. However, under-

reporting estimates have been as low as 1 percent.

Some possible reasons for under-reporting may include limitations in recognizing an adverse event, limitations in associating the event with drug exposure, and the burdens of reporting.

Additionally, there's variability in reporting. Reporting may increase or decrease with serious or notable events, with a publication of a Dear Doctor letter or with scientific or lay press publications. The year of reporting and also the length of time a product has been on the market also influences reporting.

In summary, despite the limitations of incomplete data, variability in data, and substantial under-reporting in this voluntary system, we have a system that is sensitive to rare events, that provides an excellent source of case material, and is useful for hypothesis generation.

Adverse drug event reports may be submitted when a drug/adverse event relationship is suspected. Some reasons to suspect a drug/adverse event relationship include the temporal, or the time relationship between administering the drug and the development of symptoms, a dose response, or a mechanism of action or biological plausibility, or a class effect, or the absence of alternatives, and dechallenge, or the abatement of symptoms

when the drug is discontinued, and rechallenge, the recurrence of symptoms when the drug is reintroduced. Again, dechallenge and rechallenge provide additional evidence of a relationship between a drug and an adverse event.

In 1998, OPDRA analyzed spontaneous adverse drug event reports of positive dechallenge/rechallenge cases of depression, mania, psychosis, and suicide attempt. The 1998 case series supported the Accutane labeling change, which included a warning concerning psychiatric disorders. The warning stated that Accutane may cause depression, psychosis, and rarely, suicidal ideation, suicide attempts, and suicide.

There were 20 cases in this report. 19 were U.S. cases. There were 14 cases of depression, 5 cases of psychosis, and 1 case of a mood disorder. The cases were evenly distributed between male and female. The median age was 20 years. 5 cases had a psychiatric history, and 5 patients required hospitalization.

I'm going to spend some time on this slide. This table compares the first and second course of Accutane with respect to total daily dose, time to onset of symptoms, and time to recovery. This information was not provided in every report. The n refers to the number of reports that provided the requested information.

During the first course of Accutane, there were 13 of 20 patients reporting a median daily dose of 50 milligrams. The 50 milligrams corresponds to a dose of 0.7 milligram per kilogram per day in a 70 kilogram patient.

13 patients reported a median time to symptoms of 31 days.

6 patients reported a median time of recovery of 3 days. 19 patients reported recovery. 9 reported recovering after discontinuation of Accutane, 4 recovered after completing the Accutane course, 3 recovered after discontinuation and medical intervention, and 2 recovered on a lower dose. From the first course, all 20 patients went on to receive a second course.

During the second course of Accutane, 13 patients reported a median daily dose of 40 milligrams.

12 patients reported a median time of onset of symptoms of 36 days, and 4 patients reported a median time to recovery of 3 days.

11 patients reported recovery from the second course of Accutane, of which 3 recovered after discontinuation of the medication, 3 recovered after completing the course of therapy, and 4 recovered after discontinuation and medical intervention. 4 patients reported a persistence of symptoms after discontinuation and/or medical intervention.

This is an example of a case report from the 1998 case series. This is a 19-year-old male described as cheerful with an uneventful medical history and was receiving no concomitant medications at the time of receiving Accutane. The patient had three courses of Accutane to treat cystic acne. During the first course of therapy, the patient developed depression, mood swings, and personality changes. The Accutane course was completed with no intervention. At the completion of the course, the patient's symptoms cleared.

The patient went on to receive a second course of Accutane. Again, depression, mood swings, and personality changes developed. The course was again completed with no intervention, and again the patient's symptoms cleared upon completion.

The patient went on to receive a third course of Accutane. Depression, mood swings, and personality changes again developed. The course was again completed. However, the symptoms persisted after the course was completed, and the patient was referred to counseling.

In support of this meeting, OPDRA analyzed dechallenge/rechallenge cases of Accutane-associated depression, mood changes, and suicide attempts. Spontaneous adverse event reports were reviewed for positive dechallenge/rechallenge cases. We found 41 cases.

20 cases were from the previously reviewed 1998 case series and 21 new dechallenge/rechallenge cases focusing on depression and suicide attempt were found.

There were again 21 cases in this case series. 17 of the 21 cases were from the U.S. There were 14 cases of depression, 3 cases of depression with suicidal ideation, and 4 cases of mood changes. There were 16 females and 5 males. The median age was 23 years. 5 patients reported a psychiatric history, and 1 patient required hospitalization.

Again, this slide will compare the first course and second course of Accutane. The table will compare the dose, time to onset of symptoms, and time to recovery. This information again was not provided in every report. The n refers to the number of cases that provided the information.

During the first course of Accutane, 16 of the 21 patients reported a median daily dose of 50 milligrams of Accutane. 14 patients reported a median time to symptoms of 30 days. 6 patients reported a median time to recovery of 8 days. 21 patients reported recovery. 10 patients reported recovery after Accutane was discontinued. 3 recovered after the course was completed. 2 recovered while receiving a lower dose of Accutane, and 2 recovered with discontinuation and medical intervention. 4 patients

did not report the method of recovery. All 21 of these patients went on to receive a second course of Accutane.

During the second course of Accutane, 9 patients reported a median daily dose of 30 milligrams of Accutane. This corresponds to 0.4 milligram per kilogram per day for a 70 kilogram patient. 8 patients reported a median time to symptoms of 9 days and 5 patients reported a median time to recovery of 7 days. 13 patients reported recovering. 3 reported recovery on discontinuation. 2 recovered on discontinuation and intervention. 1 recovered after the course was completed, and 2 recovered with a lower dose. 5 patients reported a persistence of symptoms after discontinuation and/or medical intervention.

An example of a case from the 2000 case series is this 18-year-old male who received Accutane for cystic acne. He was receiving no concomitant medications, and a relevant medical history was not stated.

During the first course of Accutane, the patient received a total daily dose of 80 milligrams of Accutane. The time to onset of symptoms was 29 days. The patient had developed depression and poor school performance. Accutane was discontinued, and the patient reported a clearing of the symptoms in 8 days.

The patient went on to receive a second course of Accutane. The total daily dose was lowered to 40

milligrams. The time to onset of symptoms was 5 days. The patient had again developed depression and poor school performance. Accutane was again discontinued, and the symptoms cleared in 7 days.

Therapy was later restarted at 40 milligrams every week without a recurrence of symptoms.

When you combine the 1998 and the year 2000 case series, we have 41 cases of positive dechallenge/rechallenge. During the first course of Accutane, 29 patients reported a median daily dose of 40 milligrams. 27 patients reported a median onset of symptoms of 30 days, and 12 patients reported a median time to recovery of 4.5 days. 40 patients reported recovery. Of the patients reporting recovery, 19 recovered after Accutane was discontinued. 7 recovered after the course was completed. 5 recovered with discontinuation and medical intervention, and 4 recovered on a lower dose of Accutane. All 41 patients went on to receive a second course of Accutane

During the second course, 22 patients reported a median daily dose of 30 milligrams. 20 patients reported a median time to symptoms of 10 days, and 9 patients reported a median time of recovery of 7 days. 24 patients reported recovery, and 10 patients reported a persistence of symptoms after discontinuation or medical intervention.

2 patients recovered on a lower dose.

In summary, we have 41 Accutane associated dechallenge/rechallenge cases. 76 percent were without a reported psychiatric history. The median time to onset of symptoms during the first course of Accutane was 30 days, and a median recovery time of 4.5 days. During the second course, or the rechallenge course, the time to onset of symptoms was shorter in the cases that provided the information. Also, after the second course of Accutane, depression persisted in some patients after discontinuation of Accutane and/or medical intervention. There was a possible dose-response to Accutane observed in 6 patients.

In conclusion, dechallenge/rechallenge cases provide strong evidence to support a link between a drug and an observed adverse event. We have presented 41 cases of positive dechallenge/rechallenge which provide further evidence to support a relationship between Accutane and depressive symptoms.

Thank you.

DR. BERGFELD: Thank you.

We're going to take the questions during the discussion time.

Moving on to the next presentation by the FDA, Diane Wysowski, Postmarketing Experience Suicide and Depression.

DR. WYSOWSKI: Today I'll be summarizing reports that FDA received of suicide and depression in patients treated with Accutane. Reports are from the United States only with Accutane as the suspect drug entered in the FDA's database from marketing in 1982 to May 2000.

Over the 18-year period of marketing, the FDA received reports of 37 U.S. patients who committed suicide, 24 on Accutane and 13 after stopping the drug.

Individuals who committed suicide were mostly male. The median age was 17. The median time on Accutane to suicide was about 3 months. For individuals who committed suicide after stopping the drug, the median time to suicide after stopping Accutane was 2-and-a-half months.

22 percent of suicide cases were reported to have a psychiatric history. About 57 percent had other possible contributing factors for depression. These included personal relationship problems, stressful life events, substance abuse, family history of psychiatric disorders, and others. Together, 62 percent were reported to have either a psychiatric history or possible contributing factors. About half of the reports, 49 percent, were received in 1998 after suicide and depression were added as a warning to the product labeling. The median peak dose was 1 milligram per kilogram of body

weight per day, which is within the U.S. recommended dose range for Accutane of .5 to 2 milligrams per kilogram per day.

In addition to the suicides, the FDA received reports of 110 U.S. Accutane users hospitalized for depression, suicidal ideation, and suicide attempt, 85 on Accutane and 25 after stopping the drug.

Individuals hospitalized for depression were more likely to be female. The median age was 17. The median time on Accutane to hospitalization was about 1 month. For those hospitalized after stopping the drug, the median time to hospitalization after stopping Accutane was 3 months.

44 percent were reported to have a psychiatric history. 52 percent had other possible contributing factors for depression, and together 69 percent had either a psychiatric history or possible contributing factors. 41 percent of reports were received in 1998, the year depression and suicide were added to the labeling. And the median peak dose was 1.1 milligram per kilogram of body weight per day.

About a third of patients had positive dechallenges with psychiatric treatment, and nearly a third experienced persistent depression after drug discontinuation. One person had a positive rechallenge,

while three others were rechallenged and were able to continue on Accutane with alcohol abstinence, dose lowering, and continued use of an antidepressant.

As of May 2000, the FDA received reports of 284 U.S. Accutane users with non-hospitalized depression. 45 percent were received in 1998 after depression and suicide were added as a warning to the labeling. About half of the non-hospitalized patients reported accompanying side effects such as dry mucous membranes, headaches, hair loss, and joint and muscle pain. About 50 percent of reports were from consumers and relatives, a higher proportion compared with most reports for most drugs.

The top 10 adverse events reported for Accutane include depression that ranks number 6.

Of course, the degree of under-reporting is unknown and may be quite substantial.

There are several pieces of evidence supportive of a possible association between Accutane and depression and suicide. These include the relatively large number of reports of serious depression, more than for most drugs in the FDA's database, the temporal association between use of Accutane and onset of depression, positive dechallenges in individuals who felt better once Accutane was discontinued and psychiatric care was obtained, and positive rechallenges in individuals who experienced symptoms again

after restarting the drug.

Also, some individuals had no reported psychiatric history or possible contributing factors, and there are similar case reports of depression and suicide in Accutane users in the medical literature.

However, there are several complicating factors. Some individuals had previous courses of Accutane without depression. There are high rates of depression and suicide in the teen years, making the independent contribution of Accutane with depression difficult to assess. And many cases had a psychiatric history and other factors, including acne itself, that could have predisposed them to depression.

Also, most serious cases did not improve with Accutane discontinuation alone. Psychiatric intervention was frequently required.

Lastly, a large retrospective cohort epidemiological study, referred to as the Jick study for the principal investigator, Susan Jick, that was funded by Hoffmann-LaRoche, found no increased risk of depression in individuals prescribed Accutane compared with those prescribed antibiotics for acne. However, the study had some important limitations.

Patients were not interviewed, so depression was under-diagnosed and under-ascertained.

The study did find an increased relative risk of 2 for suicide attempts and suicides in patients prescribed Accutane. The relative risk had wide confidence intervals of 0.4 to 10, and was not statistically significant. It's possible that a larger sample size could have resulted in a statistically significant relative risk with Accutane.

That brings me to my next point, the lack of data on acne severity or the patients' perceptions of acne severity. This is an important potential confounding variable for an association with Accutane.

There also were no data on dose collected. The recommended dose of Accutane is higher in the United States than in the United Kingdom and Canada. So, the results from these two countries may not be applicable to the United States.

Further, the U.S. data, that was included in the study but was not mentioned earlier, did not include information on outpatient diagnoses, data on deaths after 1990, and data on antibiotics used only for acne.

Finally, the investigators reported only the combined number of suicide attempts and suicides, and it might be informative to know the number and rates of suicide by drug to determine if any exceeded the population rates.

Because of these problems and limitations, we believe the results of the Jick study are inclusive.

So, in summary, the FDA has received reports of suicide and serious depression in U.S. Accutane-treated patients. The case reports are suggestive of an association with Accutane, but do not allow definitive determination as to whether Accutane causes depression and suicide in treated patients.

DR. BERGFELD: Thank you.

Our last presentation from the FDA is by Dr. Kathryn O'Connell, Biological Plausibility and Risk Management Options.

DR. O'CONNELL: Good morning or almost afternoon, everyone. My name is Kathryn O'Connell. I'm the medical reviewer in the Division of Dermatologic and Dental Drug Products, the medical reviewer for Accutane.

As Dr. Bergfeld mentioned, I'm going to be talking briefly about this, but mostly I want to concentrate on the second talk, which is risk management, because that's actually why we're here today.

I think that you've heard from the sponsor's presentations and from ours that spontaneous reports can generate a signal, but when the thing that you're studying has a high background rate, you don't really expect them to give you a definitive answer about causality. We're really

not here today to ask you as a committee to tell us if there's a causal relationship here. The sponsor has tried and we tried, and we already know that we can't do that. The real question here today is what do we do with the information we have to convey the information we have to the people using the drug and how perhaps we can resolve the uncertainty.

So, in the first talk I want to just talk about a few things that we think about when we try to decide if the inconclusive signal that's generated from spontaneous reports warrants further investigation. On the next slide, I'm only going to cover two topics that have been alluded to already, so I don't think we have to spend a lot of time on it.

The first thing is we asked ourselves are there any published cases of psychiatric adverse events occurring in association with Accutane, and the second thing we asked ourselves, are there any elements of biologic plausibility? I'm going to use this in a broad sense. Are there any elements of biologic plausibility that would worry us, that would cause us more concern?

So, the first topic, published case reports, is easy. It's one slide. These are the references so that you have them on the slide. You can read them. They range from 1983 to the papers that Dr. Byrne referred to earlier

in 1998. These are only cases of depression. There are some published things in the literature about other psychiatric diagnoses, but the vast majority are depression. We've already referred to some of these papers, and I'll just talk a little bit about them as we go on.

The second thing that I said I was going to cover on the next slide was elements of biologic plausibility. As I said, I'm going to use this in a broad sense. It doesn't mean that I'm suggesting mechanisms here. The question here is that are there things that we know about retinoids that make it not implausible that Accutane could have something to do with psychiatric illness.

So, the four issues I'm going to talk about are do we see similar adverse events with pharmacologically related substances -- different drugs, but pharmacologically related substances -- that bind to the same physiologic receptor, which is obviously in this case the retinoid acid receptor.

The second thing we want to ask ourselves, is there any evidence for a dose effect? I'm not going to say much about that because we've already heard something about that.

The third thing is whether the temporal

association that we've all talked about here already -- you ask yourself is it consistent with the pharmacokinetics of the drug, and we do know a fair amount about the pharmacokinetics of the drug.

Then the fourth thing we ask ourselves is, is there any reason to believe that retinoids would have anything to do with the central nervous system. We obviously don't have time today. We could spend a whole day on biologic plausibility in that sense, but we won't. We'll spare you.

If we go to the next slide, the first item that I mentioned was we ask ourselves, do we see psychiatric adverse events? Have they been reported with distinct substances that bind to the same physiologic receptor? Dr. Byrne and several other people have already referred to the fact that it is known that high dose vitamin A, hypervitaminosis A, has been associated with psychiatric adverse events. The first reference that I gave you there is actually a case where the indication for using high dose vitamin A was acne. It's a very complete case report by Dr. Restak that was published in 1972.

The second substance is etretinate, which is a systemic retinoid which is used in the treatment of psoriasis. The first reference that I gave you there is a very detailed reference. It describes an aggressive

personality change, profound depression, with a positive dechallenge with dose reduction. And the second reference there has three very brief little case summaries, all of which I believe had a positive dechallenge.

The third one is the only one I'm going to spend a little bit of time on because it came from a published trial. It was a trial where these investigators added a high dose of all-trans-retinoic acid to an established regimen of interferon-alpha and low-dose ara C to treat chronic myelogenous leukemia. The title of the paper is The Unexpected High Incidence of Severe Toxicity. It's important to note here, as Dr. Turner actually alluded to, is that there is a fairly reasonable body of evidence that interferon-alpha itself may be associated with depression.

But if we look at the next slide, I think this study is interesting because the column furthest over here where it says "No ATRA" means that those were the patients that got the ara C and the interferon. Then the other column, the first column, is where they got the interferon and the ara C, but they added the high dose all-trans-retinoic acid. You can see that even with the imbalance between the arms, the arm with the ATRA being less subjects, there's a pretty impressive difference in the occurrence of depression, psychosis, headache, pseudotumor,

and then overall CNS effects. There was a case of ataxia and just a variety of other things. But again, interferon itself has been implicated in depression. The authors actually suggest that there was some sort of synergistic process going on here.

So, on the next slide, we're going to move on to the second topic I mentioned which is we ask ourselves, is there any evidence for a dose effect. Again, I'm not going to spend time on this. We don't have a lot of time. The dose effect is clear for vitamin A. That's why it's called hypervitaminosis A. Normal intake of vitamin A doesn't cause these problems.

For isotretinoin and etretinate, as we've heard today here, there are isolated case reports that suggest a possible dose response. And I want to emphasize this because I don't want people to go out here and say, oh, if I just reduce the dose here, everything is going to be okay. We don't know that. You cannot establish a dose threshold. It cannot be ascertained from spontaneous reports for the reasons that everybody has already pointed out here today. The spontaneous reports are incomplete and it just doesn't allow that kind of clinical judgment to be made. All right. So, that's the dose effect.

On the next slide, the third element that I wanted to consider was whether the pharmacokinetics of

Accutane is consistent with what Dr. Pitts and Dr. Nelson presented about the offset of the symptoms when you stop the drug. We know that the terminal elimination half-life of Accutane is 10 to 20 hours. So, what I want to show you is that the pharmacokinetics of Accutane are actually consistent with the observed time to resolution of the psychiatric adverse events that we've observed in many patients upon drug discontinuation.

On the next slide, this is from Dr. Nelson's report that he spoke about earlier. He noted that a majority of the substantive mood disorder cases had offset within 30 days and that most of those occurred within 15 days. I think he mentioned of the cases that he selected to analyze, for 25 cases with both onset and offset within 15 days, 23 had resolution within 7 days and 17 of those actually had resolution within 4 days, which is remarkably consistent with what Dr. Pitts just presented where I think it was 4.5 days.

If you look in the published cases about time to offset, the most useful data -- actually the paper has already been referred to I think by Dr. Byrne and perhaps by the sponsor as well that was published by Scheinman, et al. in 1990. I want to emphasize that this was not a trial done to examine the psychiatric adverse events of Accutane. This was just 700 patients -- I believe it was an NIH trial

-- that had received Accutane for various indications. It wasn't even all acne. 7 patients in that group had enough psychiatric problems to come to attention. Let's put it that way. But of those 7 patients that they reported in this paper, it's notable that the symptoms in all 7 of them resolved within 1 week of stopping Accutane, and 1 of the patients was rechallenged and did have a positive rechallenge.

There's another paper published by Hazen, et al. in 1983, earlier. Again, this was not a trial to study this. This was just 6 patients who presented with enough symptoms to come to attention out of 110 patients. This paper doesn't actually state the exact time. It just notes that of these 6 patients, 5 continued the drug despite the depression, but that when the treatment course was over, their symptoms rapidly resolved upon discontinuation.

The last thing I wanted to talk about was biologic plausibility in the sense that I think Dr. McLane was referring to it, which is the more classic sense. We don't have time, like I said, to go into this today. He's mentioned some of the data that already exist, so I won't repeat it.

But the fact of the matter is we do know that retinoids enter the central nervous system. We know that. We know that retinoid receptors are present in adult brain.

As has been alluded to earlier, much more is known about the role of retinoids in the development of the fetal brain than is known about retinoids in the adult brain, but data are emerging. It's a very active field of research, and we know that the substance gets in. We know that the receptors are there.

The other thing I want to point out is that the psychiatric adverse events that are reported with Accutane aren't occurring in isolation. There are other adverse events that occur with Accutane, as with all drugs. If you look at the organ system categories that adverse events are categorized into, there are 28 of them I believe. For Accutane, the central nervous system, interestingly, ranks second only to psychiatric in the highest percentage of serious adverse events -- serious adverse events -- in the Hoffmann-LaRoche postmarketing database for Accutane. So, I think it's clear that Accutane affects the central nervous system.

But on the next slide, I want to make it very clear that when we use biologic plausibility, we're using it in the sense that it's not biologically implausible. There's no evidence we know of that makes it biologically implausible for Accutane to affect the central nervous system. We don't know a mechanism for the psychiatric adverse events observed with any of the retinoids, as I

think Dr. McLane already pointed out, but that an association is not biologically implausible we're pointing out.

The bottom line here is that none of these elements that anyone has described this morning or that I'm describing right now -- none of these elements of adverse event assessment nor their totality proves -- proves -- in a rigorous sense that Accutane causes psychiatric disease. But we're very concerned about the data that's been presented this morning.

This is another paper that Dr. Byrne already referred to. I think this was three cases that actually Dr. Bravard and his colleagues reported in 1993. In the last sentence in his paper, he advised us to be vigilant. So, that's really why we're here today. We want to explore what we need to do to be vigilant. What's appropriate, what's feasible given the information that we have and how might we go about resolving the uncertainty.

The last part of this is risk management and assessment, and I'm still Kathryn O'Connell.

(Laughter.)

DR. O'CONNELL: Same division. That hasn't changed.

So, if we go on to the next slide, I just wanted to tell you briefly what the regulations are

regarding this type of situation. The thing to focus on here is the word serious. This is the regulations for when you do a labeled warning, when you put a warning in the label. The thing to focus on here is the word "serious." It should be something serious. And that as soon as there's reasonable evidence of an association and that a causal relationship need not have been proved. So, this is basically the situation that we're in.

On the next slide, as you know, in 1998 the sponsor voluntarily dealt with the inconclusive evidence and put this warning into the labeling. "Accutane may cause" -- "may" used in the sense that we do not know -- "cause depression, psychosis and rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events."

So, on the next slide, I'd just like to briefly outline sort of a paradigm that we might use to discuss this today, and I think the sponsor has already talked about this this morning. I want to point out that even though we're suggesting some ideas for how we might manage the uncertain risk, we're not limiting you to that. We're here to get your advice. These are just some things that we've been thinking about and obviously the sponsor has

been thinking about.

We see it as really two goals. The first goal is short-term. We've got this data. What do we do with it? How do we manage the uncertain risk to make the use of the drug as safe as we can for patients?

And the long-term goal is really how to resolve the uncertainty. We think it's important to resolve its uncertainty, especially because it's been suggested, as you've heard over the last two days, that there's the idea out there that perhaps the psychiatric disease that we're witnessing is somehow due to the indication for the drug and not to the drug, due to the acne.

I think Dr. Jacobs did a thorough job this morning of pointing out the very important difference between serious psychiatric disease diagnosis and what really is a normal situational response probably to a very stressful situation. I'm not going to stand here and trivialize the suffering that severe acne causes, but suffering is not synonymous with a diagnosis of severe psychiatric disease.

We are aware of no adequate evidence that acne, even severe acne, causes the diagnosis of severe depression or serious depression. But if, in fact, acne contributes to it or can cause it or whatever, then the last thing you would want to do, if there's no causal association with

Accutane, is stop a drug that can, in many patients, cure the acne. On the other hand, if Accutane does belong on the list of many drugs that have been implicated in causing psychiatric disease, then not stopping the drug could have very morbid or even fatal consequences. So, we think it is important, in this case especially important, to try to resolve the uncertainty.

So, if we go on to the next slide, how do we manage the uncertain risk? There are two main topics that we'd like you to consider. What kind of information or education for prescribers, patients, or parents might help us out here? What would be appropriate given what we know? The second main item would be intervention. What kind of interventions might be appropriate, given what we know?

The types of information. We've already had an outline this morning of some of these. CME programs for health care professionals and further changes to the professional labeling over what we already have.

For patients, we could think about a patient package insert, which is optional, as you heard this morning in the first talk. There already is a brochure. The sponsor has a brochure for Accutane already, and the brochure actually does mention the warning for psychiatric disease. Are there things that we could do to that? And then the medication guide concept that was discussed this

morning.

Then the third item under this menu here of information and education would be perhaps some sort of informed consent process.

On the next slide, the intervention category would include things like monitoring of patients, management, advice about how to manage the events, and drug distribution. Again, we're putting everything up here that would fall into these categories. This doesn't mean that we think that everything that is up here is appropriate or reasonable given the state of our knowledge. We just want you to consider all the possibilities.

On the next slide, we go to the final topic which is really how might we resolve the uncertainty. It's clear from what we all heard this morning that we're not going to resolve the uncertainty with spontaneous reports. I'm not going to spend a lot of time on this because I think the sponsor has already done a very good job of outlining the problems that we face in trying to get a handle on this with the gold standard, which is, of course, what everybody would like to see, a prospective controlled trial. But the issues that have already been mentioned are very real. How do you mask that trial? How do you control that trial. How do you avoid the bias of patients giving informed consent to be in a trial for a drug they know

works for a very bad disease, but they're worried, oh, if I tell them I'm depressed, I'll be discontinued? So, there are a lot of problems here.

The other thing we'd like you to think about is what kind of basic science research might help us, again another open cohort study. This we would think of in terms of collecting more data about what is actually occurring, what are the characteristics of the cases to really form hypotheses to inform more formal types of studies? And then a well-powered, retrospective epidemiologic cohort study are really the four categories that we've come up with.

So, basically that's the end of my talk. Oh, it isn't the end of my talk. I'm sorry. I'm telling you stories. One more slide.

I just wanted to point out that there are some clinically important questions, really clinically very practical questions, that a formal study might answer. Again, there's no guarantee it would, but if it did, I think clinicians and patients would be very grateful. The first obvious question is, is there a dose threshold? That would be wonderful. If there is a causal relationship, which we don't know, but if there was, if there as a dose threshold that was still within the minimum effective dose for acne, we would have solved our problem.

Another practical question. Is there an identifiable subset of patients at increased risk? Then we don't have to apply risk management to everybody. We just apply it to the people who need it.

Another question that I think people out there actually using this drug would very much like to know is, if symptoms do occur in this setting, is a dose adjustment or addition of treatment with antidepressants safe, or do you really have to discontinue the Accutane, which obviously has consequences for the patients who have severe acne that can lead to scarring if they don't get effective treatment?

So, now I really am finished with my talk. The last slide up here is just all of these items on one slide, if you'd like to use that during your deliberations.

DR. BERGFELD: Thank you very much.

We're going to move now to the open public hearing. Again, to set the stage and the rules of order, each of the presenters has been allowed a specific amount of time. Three of the presenters have been allowed 5 minutes and one 20. We'll ask you to stick to these times. We will run a timer.

After the presentations, we will adjourn for lunch and then reassemble 30 minutes later.

Our first presenter is Margaret Hager. I would

like you to introduce yourself, who you represent, and if you have a conflict of interest.

DR. HAGER: Good afternoon, everyone. I think it's afternoon by now. My name is Margaret Hager, and although I am an M.D. family doctor, I'm speaking today as a mother.

In 1991 in my son's junior year at Princeton, treatment was commenced with Accutane for cystic nodular acne by a local dermatologist. During the second course of treatment, Chris developed severe headaches and dizziness. He was seen by a neurologist who advised stopping Accutane.

During this time and after cessation of treatment, although the headaches abated, Chris began with severe treatment-resistant depression, with two hospitalizations for suicide intent. Despite excellent psychotherapy and full therapeutic trials of numerous antidepressants, Chris' response, with the exception of a few brief periods of remission, has been only partial, resulting in his being homebound and on disability.

Three years after the onset of his depression, Chris developed bouts of acute recurrent pancreatitis and was subsequently diagnosed with cystic fibrosis, pancreatic mutation. My educated hunch is that if this depression is Accutane-induced, it may be due to an interaction of the chloride ion channel defect of cystic fibrosis with the

drug, and this might point the way to a vulnerable subset since the carrier state is very prevalent.

My question to the psychiatrists present is this -- and I think Dr. Byrne answered one of these questions -- have any specific characteristics been identified in Accutane-induced depression? And have any particular antidepressants or combinations thereof been found to be more efficacious in this kind of depression? Have you seen depression such as this one associated with Accutane and persisting long after the drug has been stopped, suggestive of permanent neurological damage?

Chris and I agree that if we had known that he would exchange a cosmetic problem for mind-destroying depression, we clearly would have chosen the former. Thank you.

DR. BERGFELD: Thank you.

Our next presenter, Kimberly Smith.

MS. SMITH: Thank you and good afternoon. My name is Kimberly Smith. I'm 36 years old, and I'm here today as an Accutane survivor. Even though I'm grateful to be here, I know full well that this will probably be the most personally humiliating presentation I ever make.

I went on Accutane November 4th of 1998, and I was on Accutane until April 26 of 1999. I went on 40 milligrams of Accutane a day. My dermatologist said to me

that this was the most safe and most permanent drug used in treating adult onset cystic acne, which is what I was diagnosed with. He said that he had been involved with the pretrial studies and had been working with Roche Labs for many, many years and he had an excellent track record with respect to Accutane.

Six months later, after the Accutane treatment was over, my acne was gone, completely clear complexion. But the problem was, in the meantime, it had completely devastated and almost destroyed my life.

Before Accutane I was very driven, goal-oriented, high energy, extremely positive, passionate about life and people, lots of friends. I was in a serious relationship. We were talking about getting married. I was very motivated. I put myself through undergraduate at the University of Delaware. I also put myself through graduate school at Northwestern University.

By the time that I had started my Accutane therapy, I had risen to the top of my profession. I was the Executive Director of Strategic Marketing and Client Development for a large law firm in the City of Chicago. This was also an industry that I had also helped pioneer 10 years earlier. It's called legal services marketing. When I got in the profession, there were about 15 to 20 of us. Today the profession has grown to over 4,000. I was the

only non-lawyer appointed to the executive committee of a management team of a law firm, which if you know anything about the law firm structure, this is a fairly unique position, as most of the executive members are attorneys and partners. I was making well into the six figures and very well compensated for my effort.

I had a love of exercise. I was very physically fit. I ran between 25 and 30 miles a day. I even ran a marathon. Loved to dance. Had an adventurous spirit. I earned a dance scholarship to fund part of my undergraduate degree, and also when I moved to Chicago and thought it would be an interesting way to initiate myself and make a life in Chicago, I as a part-time endeavor was a cheerleader for the Chicago Bull's first season and then went to graduate school while I was working.

When I was diagnosed with the adult onset acne, the dermatologist that I had been seeing did tell me about the pregnancy issues. He asked me if I was planning to have a child within the next year. I told him absolutely not, that that wasn't a problem. I read a pamphlet and I signed a consent form, and that was the end of our discussion.

I did ask him if there were any other side effects that I should know about, and he told me that I may experience dry lips, chapped skin, dry skin, eczema, and he

also said peeling feet, which in fact I did get. But he assured me -- and this was probably the biggest safeguard -- that whatever happened would end as soon as I stopped taking the drug. And given his considerable history with the drug, I felt very confident. I thought it was a miracle drug. Great, six months this is gone, and I was a very eager participant.

One month later, my behavior changed dramatically. I went from this very determined, strong-willed person to this confrontational, edgy, stressed beyond imagination person. Indicative of this, I impulsively resigned my position I think it was December 8th. So, it was a little a month over after the Accutane. This happened to be eight days before my annual bonus, which was fairly sizeable. Trust me, in a rational moment I would have never walked away from an annual bonus that was part of my salary.

Fortunately for me, the firm rejected my resignation, and life continued. But the problem was my behavior worsened. I went from angry at the world, withdrew from friends and family, relationships spiraling downward, no desire to talk to people. I was very short. But then it grew into a position where I started to feel a major lack of confidence, self-esteem issues, memory problems, inability to focus, difficult sleeping. And then

ultimately thoughts of suicide occurred. Mine were never violent thoughts. It was basically thoughts of how good it would be to not exist anymore, that I didn't offer value to anyone. I was ineffective and just basically believed that overall I was completely worthless.

I saw my internist on February 11th of 1999. I told him about my problems with depression and anxiety. I never thought anything about the Accutane and never did throughout this entire time. Never linked it. So, I told him about this. And fortunately, my internist had been my internist for about 10 or 12 years at that point in time, so we had a very long-established relationship.

I was blaming most of my problems on my job. He suggested that I go on to Serzone and also suggested that I take a short disability from work, which I did. I felt like a total loser.

My boyfriend at the time took me to Mexico. He thought some time in the sun would help. We went down for a three-day trip. The trip was extended to seven days. The trip was extended to 10 days. And I could not get out of my seat. I laid there on the beach with about seven blankets over top of me, miserable and crying the entire time that we were there.

Physically speaking it was horrible. I have severe abdominal pains which no one to this day can address

for me. I've been to see two internists, an endocrinologist, a gynecologist just for the abdominal pains alone, and they've not been able to tell me what the problem is or recommend a treatment.

I have a loss of appetite, which I still have to this day. I do make myself eat, but to be honest with you, I have no craving to eat.

I had a bleeding rectum for which I endured two rectal surgeries.

An overactive bladder. I'm with my second neurologist trying to discern why this is the case.

Severely dry skin and eczema which exists to this day.

Aching bones, which I still have, which prevent me from running as I used to do.

Sensitivities with my teeth and gums.

Major headaches.

And I would vacillate between insomnia and then overall just fatigue.

On March 15th, 1999, I got a call from Roche Labs, and it was completely unexpected. But what I had done is I had elected to participate in a post Accutane study, during which I had identified the fact that I was depressed, not necessarily knowing that this was necessarily the reason, but I did disclose this.

Oh, you know something? Hold on. Let me step back. I apologize.

On March 15th, 1999, I didn't get a call. The call did not come from Roche. It was a year later.

On March 15th, 1999, I got a phone call from a long-term friend who just called to check up on me to see how I was doing. During the course of our conversation -- she had known that I was on the Accutane and she didn't know the depths to my despair. At this point in time, I was on disability from work. She told me that there's a tremendous amount of people -- she lives in New York -- that she knows and that many of them had been depressed and they had all been on Accutane. So, that was the call, her phone call.

The next day I immediately called my internist and went to see my internist. This was about 5 weeks before I stopped my Accutane treatment. My internist told me that based on his information and the relationship that we had, he said it's a good thing that I knew you before you were on the Accutane. He said this was definitely the cause of the depression. And I said, well, there's good news. My dermatologist has assured me that all the side effects go away with the cessation of Accutane, and I was very convinced that that would be my experience as well.

So, he put me on Serzone. He also suggested

that I go see a therapist, which I did. And I believed all would be fine and great when everything was done.

I went to my dermatologist. I told him of the depression that I had experienced, and he thanked me for ruining his perfect record. He said that he had heard of people that had been depressed and that, essentially, he felt that everything would change in a few weeks. So, I believed him.

A few weeks later, I did stop the Accutane. 10 days later, I impulsively quit my job, this time for good, thinking that it was the job stress, not necessarily the Accutane.

As time went on, I struggled for the following year trying to get a job, thought that it wouldn't be that difficult. Of course, I'm this driven person. You just go out and get one, and the reality of the situation was, I had no confidence, I had no self-esteem and a complete inability to focus.

DR. BERGFELD: I'll have to ask you to close.

MS. SMITH: Okay.

I did receive a phone call the following year from Roche Labs, and it was February 18th, 2000, following up on the survey. During that time, I had told them of my bouts of depression. She already knew that. I asked for additional assistance, if there was any programs that she

could recommend, if they had any information. No information was available.

I had been on the drug during the time at which the FDA talk papers and the Dear Doctor letters had gone out. I got on the drug November 1998 and was on until April 1999, never received any new warnings. This was completely devastating to learn that while I was talking to the Roche representative, I told her that my reason for participating in this was that I was hopeful that stronger warnings could be put out so that it not affect people in the future. She told me that I should be really happy, that she had a new warning label, and I asked her to read it to me.

It was from that that I was absolutely shocked, did my own research, started talking to other people, and have subsequently found that this depression and these serious effects impact a lot of people. The unfortunate part is they, like myself, have no idea that it's at all related to Accutane. There is no information out there, and most of them go unreported. I know 11 people that I can talk about just right now, if that were the case, that I could tell you they have not reported their symptoms.

I'm hopeful in the future. Like I said, this drug did cure my acne. Even if I had known about the side effects, I may have gone on the drug. Who knows? But at

least I would have been able to assess and experience, as these side effects were persisting, what they were, and I could have received the proper help.

Thank you.

DR. BERGFELD: Thank you.

Our next presenter, James Palazzolo.

MR. PALAZZOLO: Good afternoon. My name is Jim Palazzolo. I'm here today to express my concern that more may need to be done to make drug companies report foreign adverse events.

For example, how could it be that the French government warned about psychiatric adverse events 11 months before Hoffmann-LaRoche enhanced its warnings here in the United States?

My son Chris took his own life July 1st, 1997 while on Accutane, 8 months before the warnings were enhanced in the United States and 4 months after the warnings were made public in France.

Here in the United States, it is mandatory for a person who is prescribed Accutane to take a blood test for liver disorders, and women must take a pregnancy test because of birth defects. Why not make it mandatory for people on Accutane to be monitored on a psychiatric basis? It is my experience in the past that physicians have not taken psychiatric events associated with Accutane

seriously.

The present warnings in my opinion do not go far enough because they leave the cause and effect issue in question. There is no doubt in my heart that the appropriate study will show an adverse psychiatric connection with Accutane. I strongly urge the FDA to consider performing an independent study to confirm what I already believe, that Accutane can cause serious psychiatric side effects in some people.

Thank you.

DR. BERGFELD: Thank you.

Liam Grant?

MR. GRANT: Good afternoon, ladies and gentlemen. My name is Liam Grant. I'm chairperson of an organization called the Roaccutane Action Group.

Our group was set up in 1997 to provide support for Accutane victims, to investigate all aspects of Accutane from the initial pretrial studies to review the literature, ADR reports, physician guidelines and so on in each country throughout the world where the drug is sold, also to fund and coordinate a series of scientific studies on Accutane to determine the mechanism by which Accutane causes so many severe physical and psychiatric side effects.

The principal side effects of Accutane based on

adverse reaction reports and published studies include general side effects such as photophobia, muscle and joint pain, insomnia, lethargy, central nervous system side effects such as pseudotumor cerebri, which is described as a serious condition involving swelling of the brain, visual disturbances, hearing deficiencies, malaise, drowsiness, amnesia, hallucinations, and psychiatric disorders, which include behavioral disorders, seizures, psychosis, schizophrenia, depression, suicide ideation, suicide thoughts and actions, and also as we all know, it's a teratogen.

What is Accutane? Accutane is an analog of vitamin A. It's likened to an overdose of vitamin A. There are many published studies showing that excess vitamin A causes a condition known as hypervitaminosis A. The study I mention here is a 1972 study, and it showed that the ingestion of large amounts of vitamin A is known to cause depression and psychiatric illness. In fact, we have also reports in the 1800s and the early 1900s of groups of people with high intake of vitamin A in their diet which caused major depression and psychiatric illness.

Therefore, the manufacturers of Accutane, Roche, would have been able to predict with reasonable certainty the main side effects caused by Accutane, including psychiatric side effects and teratogenicity. And

that prediction could have been made with certainty prior to the drug ever being launched here in the United States or in other countries.

What do scientific literature reports say about Accutane? Well, there are a substantial number of published studies linking the ingestion of Accutane to the emergence of psychiatric disorders as far back as 1983, less than one year after the drug was released onto the market. I've only time to briefly refer to three of these studies.

The American Academy of Dermatology published a study in 1983 where the authors reported that 5.5 percent of patients experienced depressive symptoms while on Accutane. In the case of one 21-year-old man in that study, the symptoms of depression and forgetfulness were severe enough to cause withdrawal of the drug. So, within a few months of Accutane being introduced, the first independent study showed that 5.5 percent of patients experienced symptoms within 2 to 3 weeks of starting on Accutane.

Another published study in 1990 in the same dermatological magazine set out details of serious psychiatric disorders suffered by 7 patients where treatment had to be discontinued because of the severity of the side effects, and they were listed, including manic

depression, suicidal thoughts, fear of going insane, et cetera. And remember, that was 1990.

Another study showed that adverse drug reaction reports for Accutane in the United States in the period from October 1982 to June 1985 represented the highest number of adverse drug reaction reports received by any agency for any prescription drug. It also stated that 22 percent of adverse drug reactions for Accutane relate to central nervous system disorders, such as headache, depression, dizziness, personality disorder, and pseudotumor cerebri. Now, that's 1985.

Sales of Accutane from 1982 to 1985 were very small in the United States because of publicity on the number and serious nature of birth defects caused by Accutane at that time. Accutane at that time had been likened to thalidomide. So, Accutane with small sales at that time was attracting more adverse drug reactions than any other prescription medicine, despite the fact that some of these other prescription medicines were being sold to not just tens but hundreds of millions of people.

In 1983, Dr. Bravard and two other French dermatologists published a paper where they set out details on three different people who attempted or committed suicide which they attributed to the taking of Accutane. The study resulted in a national inquiry in France between

1993 and 1994 in Montpellier, and the study was funded by Roche. The results of that study have still not been made available to us and have never been published. That's obviously something we're pursuing at present.

In 1998, we commissioned a study in order to determine whether five other prescription medications, representing 90 percent of the acne prescription market, were showing similar adverse drug reactions to those applicable of Accutane. Dr. T. Middelkoop, who is a research scientist, investigated these five prescription medications: minocycline, doxycycline, tetracycline, Dianette, oxytetracycline.

This table shows some of the data produced in the study. Now, you first of all must remember the data is May 1998, and therefore it's 2-and-a-half years out-of-date.

The number of people prescribed Accutane worldwide, according to Roche at that time, were 6 million. The number of people prescribed the other five medications was 300 million. In fact, it was more we subsequently discovered, but 300 million. So, you can see here that there were 170 cases of suicide, suicide attempt, and suicide ideation recorded at that time in connection with Accutane treatment, which we were told was 6 million people. The other medications produced no reported case of

either suicide or suicide ideation, and 3 cases recorded for suicide attempt. And those are the medications, remember, that had been prescribed to 300 million people.

The study, which was published in 1999, also featured data for the United Kingdom. You see here that there were 23 case reports of suicide, suicide attempt, and suicide ideation for Accutane in the United Kingdom, but the number of prescriptions were shown at 12,400. The number of cases of suicide, suicide attempt, and suicide ideation for these other medications was nil. Not one case of suicide, suicide attempt, or suicide ideation, despite the fact that these other medications represent 90 percent of the acne prescription market. And yet, in this case you see 12,400 prescriptions, 23 cases of suicide, suicide attempt, and suicide ideation reports; 200 million prescriptions for the others, and no case.

The conclusion of the study was that Accutane is 900 times more likely to cause depression than the five other medications reviewed.

How many adverse drug reaction reports are there for Accutane? Well, in May 1998 Roche issued a letter to the Irish Medicines Board, which disclosed that there were 40,000 adverse drug reactions on the Roche database in respect of Roaccutane. A review of all ADR data recorded since that time suggests that there may well

now be 50,000 to 55,000 such ADR reports for Accutane on the Roche worldwide database.

Studies show that only 1 in 10 serious ADRs are ever reported. In some countries, it may be only 1 in a 100. If we apply a factor of 10 to the number of adverse reactions recorded for Accutane, we get a figure of 500,000 or more, more than half a million people, which I think gives some idea of the number of people and the scale of suffering caused by this drug.

Roche have not provided a full list of all ADRs held in the Roche database for Accutane. The FDA and other national agencies have not received this full and detailed list of all ADRs, which I cannot understand. Dermatologists who prescribe this drug on a daily basis have not got the full list of adverse drug reactions worldwide in respect to this drug. Therefore, as I speak, I don't know and I doubt if anyone in this room, apart from the Roche people, knows the total number of suicides worldwide, suicide attempt, and suicide ideations recorded for the drug and also the number, up to tens of thousands, of psychiatric disorders recorded for the drug worldwide.

I'm just going to briefly mention Norway in reference to a group of 32 very courageous people in Norway who, in 1988, set up an Accutane support group and went to the media to highlight the terrible side effects caused by

Accutane. We have the copy of the newspaper reports which are now 12 years out-of-date. They sought from the medical professional to devise proper medical treatment for people who had suffered this severe physical and psychiatric side effects which are listed in those publications in 1988.

As a result of this, the Norwegian Health Authority commissioned a study in 1992. The study was financed by Roche. The final report submitted to the Norwegian Health Authority in 1993 made no reference whatsoever to the scientific publications at that time linking the ingestion of Accutane and the emergence of psychiatric disorders and other items. They did not disclose the number or the nature of adverse drug reactions held on the Roche database at that time.

The French government health agency increased the label warnings for Accutane on the 3rd of March 1997 in order to feature suicide as a listed possible side effect. Roche did not inform the FDA or any other health agency that we've been in touch with of the increased label warnings applied by France featuring suicide as a possible side effect.

In the United Kingdom, Norway, Canada, Ireland, and many other countries, the label warning up to May 1998 simply featured possible mood change. So, people right up to May 1998 who took Accutane in Ireland, in the UK, and in

other countries, when they opened the packaging, they got a label insert. The word "depression" didn't feature or other psychiatric illness.

Most countries applied the increased explicit label warning for Accutane in February to May 1998, featuring various psychiatric disorders, which are now pretty consistent, which say, on rare occasions, suicide, suicide attempt, and suicide ideation, as well as various psychiatric disorders.

This is the only prescription medication that I'm aware of sold by a pharmacist which features on the label insert suicidal thoughts and actions as a possible side effect. And we've done extensive studies in many countries just to see is there any other product with a label warning which features suicide.

Up to the last time of checking earlier this year, the Canadian label insert for Accutane contained no reference to depression, psychiatric disorders, or suicide. The Canadian label warning simply featured mood change as a possible side effect. So, despite the existence of label warnings in France for the past 3-and-a-half years, since March 1997, featuring suicide and psychiatric side effects, despite similar type increased label warnings in the United States and other countries since the area of 1998, it seems that Roche did not see the need to upgrade label warnings

in Canada or to advise those patients in Canada who are taking this about current indications. It seems to me that since 1982, Roche applied the minimum label warnings it could get away with. Increased label warnings, of course, affect sales and they also affect profits.

Following the increased label warnings introduced by the FDA in February 1998, Roche placed advertisements in the media indicating that Accutane could alleviate depression. That was their reaction. On the 8th of March 1998, the FDA sent warning letters to Roche ordering them to withdraw the promotional material stating that they were false and misleading and promote Accutane for an unapproved use.

Roche used similar procedures or maybe tactics in the United Kingdom, but time does not permit me to just deal with those in detail at the moment.

Also, Roche used similar advertising tactics in Ireland after the increased label warnings were applied and a feature on that is by Drs. Bickers and Jacobs. And when we looked who were Drs. Bickers and Jacobs, we found that they had been employed by Roche in 1997 in order to try and persuade the FDA not to bring in increased label warnings.

It came to our attention that Accutane was for sale on the Internet. Now, as far as we can determine -- and we've been monitoring the Internet for many years --

the drug was not sold on the Internet prior to the increased label warnings, featuring psychiatric illness and suicide. To investigate the ease with which Accutane could be obtained online, we placed orders under the names of boys and girls in their teens. Within 10 days, we were supplied with the drug from South Africa with a prescription from a doctor with a South African address. Despite the restrictions for the prescribing of Accutane, such as blood tests, pregnancy tests, it is possible to get Accutane without a medical consultation. All you need is a credit card. No medical consultation. No meeting between patient and a doctor. No blood tests. No birth control safeguards. No monitoring of patients.

Now, Roche profits from sale of Accutane via the Internet could be in tens of millions and perhaps even hundreds of millions of dollars.

I would like to briefly refer to Roche pretrial studies for Accutane, which involved putting people on the medication and reporting on the results as part of the process for obtaining license in different countries, the United Kingdom, the States, different countries.

In one such study, 3 out of 76 subjects who developed adverse drug reactions to it were excluded from the results allegedly because they were dose-related. So, here you have a situation, 76 people put on the drug. 3 of

them we are told developed side effects, but they were excluded. The side effects suffered by these 3 patients have never been disclosed to us, but we have investigated them and we are investigating them, as well as other pretrial studies in other countries.

I find it extraordinary that apparently the Roche pretrial studies in so many different countries, as part of a procedure to obtain a license, did not show up depression and psychiatric side effects. Yet, the first independent study within actually months of the drug being introduced come up that 5.5 percent of people on the drug developed depression within 2 to 3 weeks. And this was followed by other studies, putting certain numbers of people on the drug and showing X percent and Y percent that they had suffered side effects, that the side effects are very real, that people who suffered the side effects were taken off the drug, psychiatric side effects taken off the drug, left for 8 to 10 weeks, put back on the drug, and then within a matter of weeks or months, those same serious side effects, including suicidal thoughts and actions, came back.

Studies need to be undertaken by Roche or dermatologists to elucidate the mechanisms by which Accutane interacts with the central nervous system and other systems in the body. This will give us an insight

into the causes of the specific side effects and hopefully leading to developing proper medical treatment for the tens of thousands, if not hundreds of thousands, of people who have suffered and continue to suffer severe side effects from this drug.

Roche have stated publicly for the past 17 years in every country -- because we followed the PR statements from Roche and they're all the same, and they haven't changed, by the way, since 1983 -- we do not know the mechanism by which this drug works. Therefore, there's no proof that Accutane causes depression or psychiatric disorders. And they have no shortage of medical people and others who will go up with this statement.

So, here we have a product. We know it causes the side effects, but why do they cause them? Well, that's not our problem. We don't know how it works. Therefore, don't ask me about the psychiatric side effects and don't ask me about all the many, many, many physical side effects. We as an organization now have to go out and are now spending our money because we know, of course, that the mechanism can be determined.

The final thing. The license for Accutane states that it should only be used for severe recalcitrant cystic acne as a treatment of last resort when all other treatments have failed. And that's the position in most of

the countries, if not all of the countries. We believe that more than 80 percent of patients prescribed Accutane have mild or moderate acne, which is in violation of the license. Prescribing doctors should be required to certify that patient's acne is within the license guidelines.

I'll just mention. There was a survey on several hundred dermatologists, conducted by a professor well-known to this side of the house, which showed that 74 percent of patients were prescribed Accutane for mild or moderate acne. We have other studies in France, and if anybody wants to have a look at them, we would provide them -- showing that between 70 and 80 percent of people prescribed Accutane have mild or moderate acne. Of course, Roche know that. Everybody knows that. It's produced for severe nodular cystic acne. Unfortunately, the FDA and other national agencies say that they really can't do anything about it. It's the prerogative of the doctor.

Patients should have all the proper tests, blood tests, pregnancy tests, and so on which should be properly monitored.

Sale of Accutane on the Internet should be immediately prohibited.

Patients should be psychiatrically assessed, using the Hamilton Scale of Depression or a similar questionnaire, before and during Accutane treatment.

Independent studies urgently need to be carried out to establish exactly the mechanism by which this drug causes so many side effects.

An appropriate medical treatment -- this is probably the most important -- must be devised to counteract the side effects and to provide treatment for the many tens and hundreds of thousands of people who have suffered severe side effects from this drug.

I want to thank the FDA very, very sincerely for allowing me to speak here today. Thank you.

DR. BERGFELD: Thank you.

The last public speaker is Richard Josephson.

MR. JOSEPHSON: Members of the committee and members of the FDA, my name is Richard Josephson. I am with a firm called Baker and Botts. I'm a lawyer and I have represented Roche on regulatory matters and other matters.

My reason for speaking with you today is a perspective that I may have that may be somewhat unique and that you haven't heard from the public sector. That is, in looking at what is before you today, I think it's first important to understand that two of the speakers, including the speaker you just heard, are involved in litigation with the company. We understand that they've suffered some personal tragedies, and I think it was important that you

be aware of that.

Second, I think that at this point in time the committee should focus again on the question that will be asked of you, in part, after the luncheon break, and that is the considerations from a risk management perspective regarding Accutane-associated psychiatric adverse events. Is there sufficient concern to justify more risk management, and what additional messages need to be communicated.

If I might point out to you just briefly, because it hasn't been brought out, but since 1986, as a result in large part of those case reports that you saw earlier and in some of the earlier papers, Roche has actually had in its package insert a statement indicating that of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy. In other words, there was an attempt prior to 1998, for almost 12 years, to capture in the adverse reaction section the depression cases, as well as the dechallenge and rechallenge cases.

After the FDA reviewed its database and ADRs in 1998, as you were told earlier, through meetings with the manufacturer, a labeling change was instituted. That labeling change has been put before you several times, but

it mentions virtually and captures almost all of the drug experience reports that had been reported to the company without regard to causation.

In addition, and I think most important, after that labeling change was made, the company began a verification process. That verification process involved a look at the entire database of drug experience reports, a pharmacoepidemiological safety assessment of adverse drug reactions. It also looked at a retrospective cohort study of databases. It also looked at a prospective analysis of the new formulation compared to the existing Accutane formulation, and there was no verification of the signal. Virtually all of the arguments that you've heard today from the FDA and from Roche indicate that at this time there has been no verification of the signal.

Nevertheless, when you consider actions that you may take or look at, you have a label currently in effect which captures the essence of the drug experience reports, even though we are sitting here today and everyone is acknowledging that there has never been a verification of the signal. This is, as you were told, unprecedented. The FDA, acting in its public health capacity, believes that that is necessary and physicians now have access to that information even though there is no verification of the signal.

If I might turn to the last slide, in law and in science we have adopted your methodologies. After years of not considering the scientific method in courts, we now have adopted from science the scientific method. If you look just briefly at the scientific method, they ask on the question of the contention of whether Accutane causes psychiatric reactions, the extent to which the theory has been assessed based on scientific valid reasoning and methodology, whether the theory has been subjected to peer review, case reports versus peer-reviewed studies, whether the theory is only based on subjective belief or speculation, whether there is a potential rate of error in this case in the adverse drug reports, and whether the underlying theory or technique has been generally accepted as valid by the scientific community.

I merely ask you to consider the fact that you now have a label, which under the scientific method, no one here can conclude that Accutane causes those effects. As you consider what remedial action, if any, is needed or additional action is needed, I only ask that you keep that in mind.

Thank you very much.

DR. BERGFELD: Thank you.

As you know, we have run a little bit late. We will take a 30-minute lunch break which will bring us back

here at 1:25. We will then proceed with the discussion and the addressing of the questions posed to us by FDA. The second part of the afternoon will then be Accutane's new formulation. So, at this point, we are adjourned until 1:25.

(Whereupon, at 12:55 p.m., the committee was recessed, to reconvene at 1:25 p.m., this same day.)

AFTERNOON SESSION

(1:27 p.m.)

DR. BERGFELD: If I could have everyone take their seat, please.

In an attempt to allow the committee to ask questions before proceeding to the questions, which are the events that we are going to do now, I would like to first call on the psychiatrists who sit at the table as part of the committee, since a lot of this has to do with their field. Dr. Andrew Winokur has asked to speak first.

DR. WINOKUR: Thank you, Dr. Bergfeld. I have three questions that I'll try to pose just in the interest of focusing the discussion.

The first, Dr. Bull, from the FDA perspective, we've heard a lot of very interesting discussion from the FDA perspective and from the sponsor perspective about the signal that has appeared that certainly pertains to psychiatric issues, especially depression, and suicide is most importantly coming out, and also from the sponsor some excellent discussions about the complexity in interpreting this in terms of the frequency of problems with depression and suicide in the population at hand.

One additional perspective that I'd be interested in, in terms of the AERS tracking system, which is part of how this signal has come to light from the FDA

perspective, I'd be interested in hearing about other drugs that have been associated with depression as a side effect. Dr. Jacobs mentioned that there are perhaps 100 drugs. Dr. Turner also referred to a number. But how other drugs that have been linked to depression are showing up on a similar tracking system so we have some sense of how the Accutane signal from the database that you're looking at fits in with other drugs that have known or suspected associations to depression as the side effect.

DR. BULL: I think in part -- and I'll ask my colleagues from the Postmarketing, Drug Risk Assessment to also speak on this issue. When we looked at our database, Accutane has a disproportionate representation for reports of depression. I think in terms of things that are alerting signals relative to what you would expect for a drug, it was, in a sense, perhaps the level of association that brought attention.

I think additionally when you look at benefit and risk and for a drug approved for acne to have serious psychiatric adverse events associated with its use in a young population, you clearly want to make sure that you are helping to do all that we can in terms of shaping the safe use of the drug so that patients for whom it's indicated that they are being sufficiently advised and managed in terms of its usage.

DR. WYSOWSKI: We did look at the rank order for depression of all drugs in the spontaneous reporting system and the Adverse Event Reporting database. For depression, Accutane ranks number 4. For serious depression, it ranks number 5, and for suicide attempt, it ranked number 10 of all drugs.

DR. WINOKUR: Thank you. That helps give a little perspective to that.

My next question I think probably Dr. McLane might best respond to this, but perhaps Dr. Jacobs would have some response as well. I was taking note of data that we were provided with about the clinical trial comparing the new formulation to the standard Accutane and the results with the BDI. I was interested and surprised to see that the baseline scores for the subjects participating in the study was 3.5, which struck me as being extremely low. We're told, for example, that a normative value in a group of college students was 12, and certainly in studies that I've seen in a cross section of a comparable age group, it's typically quite a bit higher.

This seems to go against something that we've heard about a lot over the past couple days, that patients suffering with this disorder tend to have a lot of emotional symptomatology. I'm curious as to how you all are making sense out of this particular finding.

DR. McLANE: On the Beck's Depression Inventory, it was designed originally for psychiatric patients. Many of the published materials on that include patients that are both inpatients and outpatients for that particular scale. However, there have been a number of other studies that have looked at it in different population groups. The one that you referred to we had submitted as one of the pieces of evidence within our NDA, and that was with college students.

When I had talked to actually Dr. Beck on this particular score, he had said that when he had run that study, he thought because of the anxieties and pressures of the college students, that would be an expected score. When he has looked at other normal populations, he gets scores that 5 to 10 or so for normal scores.

I think also what I would like to do is mention that on a clinical trial where you have people who are motivated to come in, that is perhaps a bias introduced on that aspect as well.

DR. JACOBS: Just to clarify that point, I also looked at the Beck scores. I think there were 60 patients who had respond yes to the assessment questionnaires. Of course, that was an average. They had low average scores. There were a few patients that had higher Beck's. What was interesting, though, is that they didn't have the symptoms

we associate with depression. They had other depression-like responses.

What was significant, though, is that there were several patients who had preexisting illness, like I mentioned before, and throughout the study, they did not have an exacerbation of their underlying disorder. There were a few patients on psychiatric meds. They had a history of being on psychiatric meds in the past. They didn't have a recurrence of it. One of the people who dropped out of the study had an interpersonal crisis as the basis for the increase in the Beck and then dropping out of the study.

DR. WINOKUR: You may want to stay there. I'll just make a comment, and then you may want to respond. I'm struck by how low that score was in this population that we've heard repeatedly is prone to experience a lot of emotional symptomatology. I'm also mindful of your comment in your presentation that especially younger people in this group, the adolescents, may be unlikely to disclose symptoms particularly related to emotional disorder.

As you well know and pointed out, this is not a diagnostic tool. It's a symptom severity rating, and I might point this out as a potential limitation of much of, if not virtually all of, the data from such studies that we've seen so far, that there's really a lack of

psychiatrically recognizable diagnostic information that we can use as a basis. Certainly symptoms help us somewhat, but unless there are data from other studies that you might be familiar with, I find it difficult to extrapolate from the data that we had seen so far to having a firmer level of understanding of the presence or absence of psychiatric problems. I think to a fair extent you made this point yourselves. So, I don't think I'm saying something at odds with your presentation. But I wonder if you have any different perspectives on that.

DR. JACOBS: First of all, as you know, the Beck is a self-rating scale and it's not diagnostic. I think certainly people who enter a study are different than people who have been either seeking treatment or not seeking treatment and may have been suffering for a different period of time.

My understanding of the literature of acne and psychiatric disorders is really having to do with symptom severity, of increasing depression, increasing anxiety as opposed to specifically being correlated with a major depressive disorder. Anybody with a vulnerability I think will have a higher likelihood of developing a major depressive disorder, which is what I saw in a few of the cases having to do with an underlying vulnerability, as opposed to taking acne in and of itself.

DR. WINOKUR: My last question is for Dr. McLane. This is related to the biological plausibility section of your talk, which Dr. O'Connell also picked up on a little bit. To be honest, I find myself a bit confused with the slide that you presented on CNS relationships with retinoids. I just wanted to pursue that a little bit farther because I think that trying to understand what biological and pharmacological sense we can make of this issue is another important part of the puzzle that we're being asked to consider.

Specifically you mentioned an association of location of some retinoid receptors with populations of dopamine systems. You mentioned some other things that made it difficult to understand the physiological or functional significance of that.

I'm wondering is there an identified endogenous ligand, and are there known pharmacological agents that act on that receptor system? And do we have any information about functionally how that system may be related to dopamine whether in terms of a synergistic or in terms of an inhibitory type function or that there's no information at all?

DR. McLANE: Let me break down your question into several parts. I think one of the first things you asked is about the receptor presence within the brain.

Specifically what they had looked at was use of messenger RNA probes. There are five different major types of retinoid receptors within the brain. The original studies were looking at embryonic brains, and there's one study that looked at the message level of these different types of retinoid receptors within the adult brains of the animals. These were the regions that they had specifically detected that message level.

A subsequent study then went in and used an antibody probe to those same proteins rather than just the message level, and found that in the brain localization many of these messengers, which would indicate a retinoid receptor was present, is no longer present as a protein. Thus, if it is not present as a protein, it would not be functional.

Your second part of your question then refers to the signaling pathways of retinoids. Isotretinoin is a natural endogenous compound that is found normally in every person. Isotretinoin is a natural ligand for some retinoid receptors. Isotretinoin has another name called 13-cis-retinoic acid. The all-trans-retinoic acid has much better binding properties to these ligands than the 13-cis does. Once the retinoid binds to the receptor, this type of receptor is a receptor that binds directly to DNA on the signaling mechanisms on genes, and it activates particular

genes.

Does that answer your question, or should I go further?

DR. WINOKUR: Almost all the way. I finally asked you if there's any insight about functional or physiological effects on, for example, dopamine systems since you did draw attention to the localization in that area.

DR. McLANE: Right. No, actually that was the point. The reason why the dopamine areas were recognized was in animals in which the genes for the receptors were specifically knocked out. In there what they saw was those animals had a change in their gate. It was reflected to their motor neuron function. On those animals, when they then did any other type of behavioral changes is when they saw the long-term potentiation changes within memory.

DR. WINOKUR: Thank you.

DR. BERGFELD: Do you have any further comments?

DR. WINOKUR: Well, the sort of additional comment from the line of questioning about the Beck is that, again, we've heard the different perspectives on the signal and the potential complications. We're clearly not going to resolve all of this. But it strikes me that part of the issue is a need for data that it sounds like are not

really available that would address some very fundamental clinically relevant questions that perhaps at some point we could get into a discussion of what kind of studies and how. But I think there are sound, thoughtful arguments on both sides of the issue of the signal. We'll hear from the other psychiatrists, but I think the lack of some just fundamental, critically important dimensions of what we would need to hear about to think about how to take things further is very striking to me.

DR. BERGFELD: Thank you.

I have on my list Dr. Malone and then Dr. Greenhill and then Dr. Byrne.

DR. MALONE: After listening to the presentations, I think it is hard to look at a disorder that has a fairly high prevalence and then find perhaps a side effect that could be clinically significant but not all that common.

But I am still impressed by there being a signal because these are things that are often under-diagnosed in every population. The only reporting was voluntary reporting. So, when you look at voluntary reporting by a group of patients who often don't talk about their symptoms, I'm impressed that there is a signal, that it means something should be looked into. I just wanted to make that statement.

Secondly, you had asked a question about other drugs that the FDA knew about that had depression and suicide. Was that data pre-1998 or post-1998 when the labeling changed for the drug?

DR. WYSOWSKI: The rank order that I gave was post-1998, but we did look pre-1998 and pre-1998 Accutane was number 7 for serious depression. So, this ranking, even if you look prior to 1998 when the labeling change came in, it was within the top 10.

DR. MALONE: I still think that is impressive.

One of the presenters, Mr. Grant, had a slide where he showed the occurrence of suicide and depression with Accutane, then the occurrence in the antibiotics. Has the FDA looked at their data regarding the rates of suicide and depression for those antibiotics?

DR. PITTS: Frank, could we put the overhead up? The one with tetracycline and Claritin.

This overhead represents the total number of cases of depression, mood alterations, and depressive symptoms with the tetracycline actually since we received reports of tetracycline. So, it's a total database, and it includes all of the tetracyclines, tetracycline, oxytetracycline, minocycline, and doxytetracycline. There were 8 cases of depression and 2 cases of suicide. One of the suicides was in an 85-year-old female and the other was

in an 18-year-old.

DR. MALONE: What I thought was impressive about Mr. Grant's slide -- I don't know where the data came from -- was the large number of prescriptions for the antibiotics versus the relatively smaller number of prescriptions for Accutane. I guess that would be true in your database also. If you're looking at trying to figure out how many prescriptions had been given versus the number of serious adverse side effects reported to the FDA.

DR. BERGFELD: Most likely that would be true because of the use in the dermatological community.

DR. MILLS: May I make a comment on that? I'm Jim Mills. This is just an epidemiologist that couldn't keep his mouth shut here.

DR. BERGFELD: That's all right.

DR. MILLS: If I remember the slide correctly, 1,400,000 prescriptions for one of the antibiotics with no suicides, no suicidal ideation. Now, you tell me that there's a population of a million and a half people anywhere in this country where nobody has any of those problems. It's a classic case of poor reporting. I personally would make absolutely nothing out of the data there for that simple reason, that you're just not getting accurate reporting at all.

DR. MALONE: Right, but if you're just trying

to look at a signal for voluntary reporting, it might point towards there being a signal that there is a difference for Accutane.

DR. WYSOWSKI: Well, if you look at the Jick study that included antibiotics, patients prescribed antibiotics for acne, they did have suicides and suicide attempts in individuals on antibiotics treated for acne. So, there was a possible twofold increase, non-statistically significant relative risk for Accutane, but again we were talking about sample size.

So, I would have to agree with Dr. Mills that it's a classic under-reporting of individuals who commit suicide or have depression with treatment with antibiotics. I think there's selective under-reporting for the antibiotic class as a whole.

DR. MALONE: Just one more comment. It's really about the use of the BDI. When I read the report that was given to us, it seemed to me that they were looking for BDI scores that were only in the severe range. I understand that this was not a clinical population coming for a depression study. I don't do depression studies, but my understanding is that they usually use the Hamilton, which is a clinician report rather than the patient report used in this study. In order to get into the studies for the treatment of depression, it would require a much lower

score than they were using in this study.

DR. BERGFELD: Dr. O'Connell.

DR. O'CONNELL: I'd like to comment on that only because we're going to discuss that trial this afternoon because that data relates to the new formulation NDA, and that's not going to help you now if we discuss it this afternoon.

I know we're incredibly tight for time here, but I just want to point out that that the objective of that trial was to study the new formulation. It was just to compare the safety and efficacy in general of the new formulation of currently marketed Accutane. The FDA did not help to design that trial to study specifically the adverse events due to Accutane.

Basically the issue was the trial was designed before the 1998 warnings but while we working up the problem. Since the investigator's brochure was essentially the labeling which didn't have the warning in it at the time, we wanted to make sure that the patients' safety was monitored.

So, I think it's very wonderful for the sponsor to look at the data from that trial in an exploratory sense to learn something about, if we do future studies, to specifically address this issue, what we might learn about design and things like that.

We can talk about it this afternoon, but there are lots of reasons why I don't really think we can use that data to really form any sort of --

DR. BERGFELD: Are you through?

DR. O'CONNELL: Yes.

DR. BERGFELD: Dr. Mills?

DR. MILLS: Even though I'm a birth defects epidemiologist, I don't see too many other epidemiologists here, so I'd like to make some general comments in the area of epidemiology.

The first is it's very difficult, as people have suggested this morning, to find an effect when there are multiple competing causes and when the condition is common. This is clearly the case here, particularly when we add in that cystic acne itself may be a cause of depression.

However, it's important, if we can, to rule out a problem here because of the high exposure. For example, the Roche people estimated that if there were no etiologic effect at all of Accutane, that just given the number of people who are exposed, that they would expect to see 150,000 cases in their population. So, in other words, if the increase because of Accutane were as small as the relative risk of 1.1, we would be talking about an additional 15,000 cases.

So, it is important to try to answer this question. A very large study would be needed to address this. I think it's going to be extremely difficult to do that. When I say "to address this," I mean either to identify an effect or even probably larger to rule out an effect.

A randomized cohort study where some people are given Accutane and some people are given a placebo would be highly unlikely to be done for several reasons. First, because of the large number and the expense that would go along with doing that kind of prospective study. Secondly, because there would be possible ethical questions and clearly difficulty recruiting people into a placebo study if they had severe cystic acne. So, I don't think that's likely to happen.

I realize I'm coming out being against epidemiologic studies even though I'm an epidemiologist. But I also think a case-control study would be very unlikely to answer the question. As Dr. Wysowski pointed out, the Jick study had some major problems and those are not easily solved. For example, you want your cases and controls to be virtually identical except for the exposure of interest, that is Accutane. But that's unlikely to happen because they're also going to have cystic acne which is a risk factor that you can't control for. So, a case-

control study is never likely to have a proper balance and be able to address the question.

Which leaves me with the suggestion that we may not be able to get a direct answer to the question how much, if at all, does Accutane increase your risk for depression or other psychiatric illness.

But I would suggest that we might be able to get some worthwhile indirect data by essentially looking at a case series or just a cohort of people who were treated. This would provide an opportunity under rigorous observation to look for the type of cases that were described this morning of people who develop the illness after treatment, and we would have the opportunity in this group to do a psychiatric evaluation prior to and then during or after treatment in order to establish that this was, in fact, incidence of new disease, not simply someone who had psychiatric problems all along.

It would also enable us to test in a more rigorous way people who have, as we heard previously, the experience of developing psychiatric disease on Accutane and then having resolution of psychiatric disease when the Accutane is stopped because this could then be studied in a very rigorous fashion while the people are treated, after the people are treated, and then they could be rechallenged.

In the unfortunate event where someone does commit suicide, we would have a much better opportunity to do the psychiatric autopsies that were discussed this morning, but I hope more likely that we'd be able to do a good psychiatric profile of the people who develop psychiatric disease on treatment to account for other risk factors, such as family history or drug abuse.

Then I think that Dr. Hager made a very interesting suggestion this morning, and that is within the cohort, if we looked at the people who on treatment developed psychiatric problems versus the ones who did not, would there be biochemical or genetic markers that we could test to see if there is a population with a predisposition. Just as an example of that, retinoic acid receptors or something along those lines would be something I think would be quite intriguing to examine as an internal nested case-control study, if you will, within this population.

None of these will give us the most critical data, which is is the risk higher of developing psychiatric disease on Accutane than not on Accutane, but they will give us some very useful ancillary information that may indirectly answer that question.

DR. BERGFELD: Thank you.

Dr. Greenhill?

DR. GREENHILL: I found the discussion today

DR. BERGFELD: Dr. Jacobs.

DR. JACOBS: Just to respond to that, in reviewing the cases of depression, psychosis, and suicide, the clarity of diagnostic information to really state it was a bipolar disorder was virtually nonexistent. I did not see any clear-cut relationship between the administration of Accutane and the production of symptoms, and then it was confirmed that the person had, for example, bipolar disorder.

DR. BERGFELD: Is there an FDA response?

DR. PITTS: Yes. I'm aware of one case where we had a diagnosis of bipolar after Accutane and another case where we had a psychosis and mania after Accutane.

DR. GREENHILL: I think that just makes me stronger in support of the suggestion by, I think, Dr. Mills for the possibility of a rigorous study with diagnostic criteria and direct interview of all the patients who might enter into such a study.

DR. BERGFELD: Thank you.

Dr. Byrne?

DR. BYRNE: I would only have about two comments.

One would be that in relation to the earlier presentation that suggested that retinoids were detectable or isotretinoin was detectable in rat brain following

administration. I feel that's probably pretty significant in relation to what I had said before.

And the other issue that I would mention is that, A, I don't know what the effect of that would be while it was there, and B, if isotretinoin can completely reverse the process that causes acne, what is the isotretinoin doing within the brain substance while it's there? That would be my only comment in real terms.

DR. BERGFELD: Thank you.

I have several people on my list. Dr. Rosenberg, Miller, King, Levin, and Branch in that order.

DR. ROSENBERG: Thank you. I have two things.

One, like a lot of many other physicians, we don't just take care of diseases, we try to assess the patient and modify the treatment depending on the special needs of the patient. While we've heard and certainly I've experienced sad, young people because of severe cystic acne, I must say that the most upset patients that we see with acne don't have the bad cystic kind. Frequently they're young people who are terribly upset over what looks to me like really not much to be that upset about. But they say, well, it's really an important thing in their lives. And you start rattling off the names of the medicines that we use. Used that, done that. Is there anything else? Then I will say, well, there's Accutane.

And I'll tell myself maybe for this patient it's worth it.

As I think about what we've heard today, are these people already suffering from some personality disorder or psychiatric disability that would place them at higher risk of a real serious reaction than the youngster with the bad cystic acne, in which case am I just asking for extra trouble by doing that? And if I am, maybe we should indicate that somehow for other people so they don't fall into the same trap.

The other thing I was going to ask is it might be doable in the laboratory with rats or something. I wonder if there's any comorbidity incurred by Accutane plus, say, either cocaine or methamphetamine or some of the things that are around out there that young people bump into. We can't ignore the incidence of that use.

Thank you.

DR. BERGFELD: I think there's a response from FDA. Dr. Bull?

DR. BULL: It's more of a procedural question. I wanted to just ask, because looking at our questions, some of these are being addressed in the discussion, and I'm sort of getting a sense that we are moving from clarifying questions to actually some that address the questions we have for the committee. A lot of this discussion has taken that framework, and I don't know

whether or not it might help us to sort of move the dialogue along if maybe we went ahead and addressed those. I don't want to in any way impede discussion, though, or any other further clarifying issues that need discussion.

DR. BERGFELD: Thank you. I think that's a good attention getter.

I think what I'll do, though, is call upon the people that I have on my list and ask them to be brief. Dr. Adams? Is that who is waving to me back there. If you don't mind responding next.

DR. ADAMS: Well, my question was one for clarity, but then I have another one that is probably more appropriate for later.

I still need clarity on the interaction between retinoids and the D2 receptor gene as to whether or not dose-response is understood in brain tissue and whether or not retinoids have the ability to up- or down-regulate the production of the D2 receptor from that gene.

DR. McLANE: There have been two studies in embryonic neural cells.

DR. ADAMS: I'm sorry. I wanted to focus my comment just on the adult.

DR. McLANE: No, there have not been.

DR. ADAMS: I would see that as an area of need.

DR. BERGFELD: Thank you.

Dr. Miller?

DR. MILLER: I'll wait.

DR. BERGFELD: You'll wait to the questions?

Dr. King? Wait till the questions?

Dr. Levin? Questions?

Dr. Branch? All right.

Dr. Lammer?

DR. LAMMER: Yes. Both Dr. Nelson from the sponsor and the FDA representatives listed among the criteria for trying to decide whether these reports might be causally linked to Accutane, one of the criterion they both emphasized was the possibility of a dose-response relationship. Dr. Nelson didn't mention anything methodologically about how he concluded that there was no apparent dose relationship, and I'm pretty unconvinced by the FDA presentation that in their conclusion isolated cases suggest a dose-response effect.

I'm really unaware of any methodological approach that allows you to take a data set composed essentially only of adverse drug reactions and come up with a dose-response relationship, one way or the other. So, I think for the purposes of the committee deliberation in trying to assess a possible causal relationship, dose-response effect here I think is just not an appropriate

criterion to be looking at, considering that we're dealing essentially only with adverse drug reaction reports.

DR. BERGFELD: Thank you for that clarification.

Dr. Malone wanted to say something before Dr. Bull presents the questions.

DR. MALONE: I was impressed with the epidemiology of depression presentations on both sides. I just had one point to ask the Roche people. In what you said, did you say that one of your plans was to increase CME about the presence of psychiatric disorders in patients that might need Accutane?

DR. ELLISON: Yes, it was. Well, let me clarify. We said that the high background incidence of the disease in the cohort from which acne patients come, depending on age, sex, and prior history, the 150,000 that you would see across dermatology in this period, is an opportunity to improve the impact of dermatology practice. So, CME should include people who have those risk factors in general, not just people who you might want to treat with Accutane, so that we don't ignore them and just focus on people who would have uncertain risk. That was the point.

DR. MALONE: Because such a thing might do more for the treatment of depression than many of the other

discussions we have if they did just a simple CME presentation on depression.

DR. BERGFELD: Thank you.

Dr. O'Connell, quickly.

DR. O'CONNELL: I just wanted to clarify that when we brought that up, we were thinking too not just CME for dermatologists, not just for prescribers of Accutane, but for health care providers who would be likely to see patients who present with the problem, in other words, psychiatrists, emergency room doctors, pediatricians, et cetera.

DR. BERGFELD: Thank you.

Dr. Bull?

DR. BULL: Once again, our framework is that all these considerations are taken from a risk management perspective. We have heard today, I think, a significant body of data, both from Roche, as well as from FDA, that I think clearly lays out issues attendant to an association of psychiatric adverse events and the use of Accutane.

Our goal is to do we all that we can, to the very best of our abilities, to manage the use of Accutane such that we maximize benefit and that we minimize the risk associated with its use.

Causation is not a necessity in this instance. I would reference you back to the regulation that was read

earlier to you by Dr. O'Connell where the standard in this instance is one of reasonable evidence, and I think clearly what we will need to frame our risk management discussion on is whether or not there's reasonable evidence for us to move forward in a more definitive way to address this issue.

So, without further ado, our first question to the committee: Is there sufficient concern to justify more risk management? If yes, what additional messages need to be communicated and in what form?

John, if we could put up the options. We're going to put back up again the slide at the end of Dr. O'Connell's presentation, and I'd like to bring to your attention to the elements here which I think are options specific to question 1 on education and information and potentially intervention. So, if we can sort of shape our discussion around those as possible options for consideration.

DR. BERGFELD: Do you want to read your second question as well so we know what we're about? And then we'll go back to the first.

DR. BULL: Okay. Question 2: Would further studies help to clarify the relationship between Accutane use and psychiatric events? If so, what kind of studies?

DR. BERGFELD: Thank you.

I'll now open the discussion for question 1. I have a list here. Should I go down it again? Dr. Miller, you wished to present on question 1 or the discussion of question 1?

DR. MILLER: Yes. We certainly need a lot more data, and we've not gotten the data to this point. I think one of the things that's apparent is that we have not been reaching all the prescribers of Accutane. The educational tools have been there, and they don't reach all the physicians as they are. I think that the educational tools have to support specific recommendations. Again, using our situation as prescribers of Accutane and also teachers of dermatology residents, it's a very varied approach with a medication that has very serious implications.

What would help me and make my practice much easier would be to have a specific form that would be dealt with with each patient that would include the pregnancy contraceptive issues, that would include the appropriate questions that I would ask from a psychiatric standpoint because I don't know what those questions are, but those questions that the psychiatrists feel are appropriate. And upon completion of that form, I would then be able to write a prescription for a patient. But the fulfillment of the recommendations would be the sine qua non for my writing the prescription for Accutane. I think this would help to

eliminate those outliers who are really not going along with the recommendations, who don't have a good knowledge of Accutane, and who are not going to be reading the literature.

This would help us immensely because I think your data ultimately is going to come from the physician. If I have those forms and they're on file and they're available to you, you're going to be able to see what I have psychiatrically, what's happened with the pregnancy issues. I think it would eliminate the capriciousness of the current approach that we're taking with a very serious drug, and I really have concerns about that and it's a drug that I use.

DR. BERGFELD: If I might intervene here, are you suggesting that the psychiatric evaluation be in part of the registry that was voted on yesterday, the pregnancy registry, the female who was entered into the Accutane therapy?

DR. MILLER: I think it should be, yes.

DR. BERGFELD: And you were then saying about the educational materials, that have been so wonderfully presented to us from Roche, that incorporated into that massive group would be something on a psychiatric evaluation.

DR. MILLER: Exactly, yes. I think we have the

specific recommendations and the educational materials would support those recommendations.

DR. BERGFELD: Dr. King.

DR. KING: I'd actually like to expand on that theme, in the sense of that all change represents both a problem and an opportunity. As part of this meeting, the three goals to address the issues of Accutane and adverse outcomes in pregnancy, this committee selected design number 3, which includes increased education of patients and prescribers, more detailed or more effective informed consent, and registration to include a pregnancy registry, surveys, external data, and more increased or more accurate or efficient pregnancy testing.

I'd like to expand on that in the sense of registration must be uniform to be most practical and useful. Exceptions and subsets will not be easily captured. You have in a doctor's office oftentimes with a dermatologist 60 patients being seen in a day, and if you have to figure out, with the various people on vacation and so forth, you really need to make it male and female all ages. It moves the monitoring from a voluntary effort to a mandatory effort.

So, the registration is more intrusive, but the cohort studies and retrospective studies and other studies mentioned do provide the opportunity to capture this, but

by extension also by including what Dr. Miller suggested, measuring depression and other CNS effects becomes possible.

Since the Accutane New Formulation studies already include a more complete evaluation of depression and other CNS adverse events, it may be that by starting the new formulation anew, we won't have black box fatigue. We will put both these new changes of the pregnancy effects and depression, the CNS effects all as an integrated package. So, oftentimes when I make change in my department, if I'm going to have a major change like a new boss, you also do some other things that may not be directly related because people are expecting change.

So, if we're going to make change, let's not piecemeal this. Let's not make it hard on Roche who has done a great job of trying to identify the issues. I don't know what the receptor is on retinoids, but I do know that hypervitaminosis A is real. So, let's try to work out some solution where we're going to have an integrated package where we can modify and integrate what Roche is already trying to do both for pregnancy and depression and CNS and by having a mandatory registration, we'll have a database that we can monitor and go forward and retrospectively select out populations. I think we're going to make it more cost effective and more likely to be followed if we do

it this way.

DR. BERGFELD: I have Dr. Abel next and then Dr. Honig.

DR. MURPHY: Can I just ask a clarification question?

DR. BERGFELD: Yes.

DR. MURPHY: From what I understood both of you to say is basically you do want an informed consent, that universal approach here would assist in the efficiency of this process, and that that would involve an informed consent for everybody.

DR. KING: Absolutely. One ticket, one show.

DR. BERGFELD: Dr. Abel?

DR. ABEL: I just wanted to comment on a couple of issues. I agree with Dr. Miller in terms of patient evaluation and that dermatologists and dermatology residents in training need to be educated on how to evaluate patients from a psychological/psychiatric standpoint. Whether or not this needs to be an official registry, I'm not sure because I am concerned about the intrusive nature of this, making it part of a registry.

The other thing is, what is the information that we need to transmit to patients about risk of adverse events? One particular issue that I'm concerned about is duration. I think we heard about the cases of depression

and suicide, and with depression there was dechallenge and rechallenge. And then there were some cases that occurred after discontinuation of the Accutane. What information do we have regarding duration of side effects? This drug has a short half-life, but is there some binding to receptors that causes concern for more permanent effects?

DR. BERGFELD: I think some of that would be answered under question 2, but certainly your thoughts can be recorded and taken up again under question 2. I think that some of it will be solved by the FDA in what they finally decide to do with our answers, unless you have a specific recommendation to make.

DR. ABEL: No, I don't, but one last question is clarification or information gathering on worldwide case reports and to what extent were these incorporated into the case reports by Roche.

DR. BERGFELD: Is there a Roche response? Were the worldwide cases incorporated in your database that you presented to us?

DR. ELLISON: Yes, they were, and they were all reported to FDA as well.

DR. BERGFELD: Thank you. And to the FDA as well.

Dr. Honig?

DR. HONIG: I just wanted to follow up on Dr.

Miller's comment, basically a plea for a standardized approach to prescribing Accutane. I was wondering if you're interested in pursuing this a little further and you stop short of perhaps recommending a certification program for Accutane prescribers, there is precedent for that for drugs approved by FDA. Tikosyn, dofetilide, the antiarrhythmic I think you heard about, is approved for use by certified prescribers of the product where they have to pass a competency checklist. I'm wondering if you want to entertain that.

I know Dr. King has already in his institution put some standard operating practices in place for his trainees that are learning to prescribe Accutane.

DR. MILLER: Yes. I think that's absolutely necessary. And we've done that within the department. We've set up standards. But I think with a medication as serious as this, with all the implications -- and we want to save pregnancies and save children -- we need something official so that there's a uniformity to this, that it's not my department and Lloyd's department individually doing it. I think it has to become official so that we're asking the right questions from a psychological standpoint so that we're doing the right things as far as the pregnancy and contraceptive issues are concerned. What I see now is great diversity in this, some people not doing it and