FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

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Gaithersburg, Maryland

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P R O C E E D I N G S

(8:30 a.m.)

DR. BERGFELD: Thank you very much, and welcome to the second day of the Accutane advisory committee. Yesterday you know that we met and we dealt with the issues of Accutane and the pregnancy prevention program. Today we are moving on to other subjects regarding Accutane, namely, Accutane associated with psychiatric events for the morning and this afternoon Accutane's new formulation.

At this time, because some of the audience was not here yesterday I suspect, I would like to go around again and re-introduce the panel members. I would like to state, first of all, that we have voting and non-voting panel members. Both will participate in the discussions, but only the voting members will address the questions and vote upon them.

I guess if we could start again with you, Dr. Dianne Murphy.

DR. MURPHY: Dr. Dianne Murphy, Associate Director for Pediatrics at the Center for Drug Evaluation and Research.

DR. WILKIN: Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug Products, CDER.

DR. BULL: Dr. Jonca Bull, Deputy Office Director, Office of Drug Evaluation V.

DR. O'CONNELL: Kathryn O'Connell, medical reviewer, Division of Dermatologic and Dental Drug Products.

DR. WINOKUR: Andy Winokur from the Department of Psychiatry, University of Connecticut Health Center.

DR. ROSENBERG: Bill Rosenberg, dermatology at the University of Tennessee College of Medicine.

DR. GREENE: Mike Greene, maternal/fetal medicine, Massachusetts General Hospital, Harvard Medical School.

DR. BERGFELD: I'm Wilma Bergfeld, dermatologist and dermatopathologist at the Cleveland Clinic.

DR. MILLER: I'm Fred Miller, Director of Dermatology, Geisinger Clinic, Pennsylvania.

DR. KING: Lloyd King, Jr., dermatology at Vanderbilt University and Nashville VA Medical Center.

DR. EPPS: Roselyn Epps, pediatric dermatology, Children's National Medical Center, Washington, D.C.

DR. MALONE: Richard Malone, Department of Psychiatry, MCP Hanneman University.

DR. BRANCH: Bob Branch, clinical pharmacology, University of Pittsburgh.

DR. HOLMBOE: Eric Holmboe, general internal medicine, Yale University.

MR. LEVIN: Arthur Levin, Center for Medical Consumers in New York.

DR. GLORIA ANDERSON: Gloria Anderson, Callaway Professor of Chemistry, Morris Brown College in Atlanta.

DR. JENNIFER ANDERSON: Jennifer Anderson, biostatistician at Boston University Medical Center and Bedford VA in Massachusetts.

DR. TAN: Ming Tan, Associate Member of the Department of Biostatistics, St. Jude Children's Research Hospital.

DR. JONES: I'm Ken Jones, Department of Pediatrics at the University of California, San Diego.

DR. MILLS: I'm Jim Mills, Pediatric Epidemiology Section, the Child Health Institute at NIH.

DR. LAMMER: Ed Lammer, medical genetics, Children's Hospital, Oakland.

DR. KODISH: Eric Kodish, pediatric ethics, Rainbow Babies' and Children's Hospital in Cleveland, Ohio.

DR. BYRNE: I'm Alan Byrne. I'm an adult psychiatrist from Ireland.

DR. MOORE: Cynthia Moore, Centers of Disease Control and Prevention, the Birth Defects and Pediatric Genetics Branch.

DR. ADAMS: Jane Adams, Department of Psychology, University of Massachusetts, Boston.

DR. BERGFELD: Thank you very much. As you can see, we have a very large group to discuss the issues at hand.

We're going to move forward then and go on to the meeting statement by the Executive Secretary, Kimberly Topper.

MS. TOPPER: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

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

With respect to FDA's invited guests, Drs. Jane Adams, Alan Byrne, James Mills, and Edward Lammer have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Adams would like to disclose that in the past she has participated in two research grants to study Accutane. One was funded by Roche and the other was funded by NIH/NICHD.

Dr. Byrne would like to disclose that he has published articles on the subject of Roaccutane.

Dr. Mills would like to disclose that he is currently collaborating with Roche on an unrelated research project. He has also written an article and attended a seminar which were unrelated to the particular matters at hand, but sponsored by Roche.

Dr. Lammer would like to disclose that in the past he has served as principal investigator on phase I and phase II longitudinal studies of infants exposed to isotretinoin in utero. The studies, sponsored by Hoffmann-LaRoche, were designed to document the developmental toxicities of isotretinoin following inadvertent human use during pregnancies in North America.

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

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

Thank you.

DR. BERGFELD: Thank you.

Our next item on the agenda is to have Dr. Jonca Bull present to us the FDA's position, reprisal of risk management overview.

DR. BULL: Good morning. Once again, I would like to begin by extending thanks to the advisory committee and everyone here this morning for their presence, for their sharing of their intellect, their time, their talents in helping us better understand and develop options for the management of certain aspects of use of Accutane.

Accutane is a highly effective drug for the treatment of cystic nodular acne. Yesterday we discussed its well-characterized risk profile as a teratogen. Today we will be discussing its risk profile for its uncertain risk for psychiatric adverse events. In 1998, the labeling for Accutane was revised to reflect this concern.

I would like, as you deliberate this morning, to revisit, as part of your frame of reference, the presentations yesterday by Dr. Victor Raczkowski and Dr. Peter Honig, first, Dr. Raczkowski's talk on risk management options and Dr. Honig's talk on lessons learned, particularly the issue of labeling changes, the effectiveness of Dear Doctor letters, the concept of labeling fatigue and that labeling and labeling changes do not necessarily equal knowledge, and that knowledge does

not necessarily drive behavior.

From a risk management standpoint, this morning we will be addressing risk management and the uncertain risk of psychiatric adverse events, specifically depression and suicide. Is more needed to educate providers and patients and their families? Is more study needed to better characterize and to minimize risk and ensure safe use?

This afternoon, for the new formulation, is there sufficient information on its dosing profile for safe and effective use, as well as delineating its relationship to the currently marketed formulation?

Once again, we welcome this opportunity for discussion as we learn from your experience, your knowledge and perspectives on these issues. We have asked for and again need your help and advice.

Now for an overview of day 2. In presentations this morning, our first FDA discussant will be Dr. Nancy Ostrove from the Division of Drug Marketing, Advertising, and Communication, who will address the topic of medication guides.

Following the Roche presentation, the FDA presentations will begin with Dr. Alan Byrne, addressing clinical psychiatric case experiences, followed by Dr. Eric Turner who will talk on drug-induced depression. Dr.

Marilyn Pitts will present a case review of dechallenge case reports, followed by Dr. Diane Wysowski who will speak on postmarketing experiences and suicide and depression.

Finally, Dr. Kathy O'Connell, along with Dr. Jon Wilkin and Dennis Bashaw, will be discussing the new formulation.

In closing, I want to acknowledge and recognize the effort and commitment by FDA's scientists in gathering and analyzing information. This involves both our Division of Dermatology, our Division of Neuropharmacology, and the Office of Postmarketing Drug Risk Assessment. They have done a tremendous job in addressing the complex and difficult issues involved in preparing for this meeting.

Thank you.

DR. BERGFELD: Thank you very much.

We're now going on to Dr. Ostrove's presentation on medication guides.

DR. OSTROVE: Good morning. As I believe you all heard yesterday, one of the risk management tools that the agency has to facilitate communications with patients about their medicines, when they receive their medicines, is called medication guide. What I'm here to do today is to give you a really brief introduction to medication guides. However, I think it's important that in order to understand this particular tool, it's also critical to

understand the universe of information that is made available to patients.

So, patients can get information about prescription drugs both before and after a product is prescribed and dispensed. You're all aware of advertisements -- I believe there was a discussion about them yesterday -- which can run the gamut from being completely promotional for a particular drug to being so non-drug specific that we don't even consider them to be drug advertisements, and we don't even have jurisdiction over them.

In addition, drug sponsors make available other promotional materials such as patient brochures or patient booklets. These also can be quite varied in content. They are supplied to health care professionals, often for distribution to patients.

Now, even though we regulate the content of these materials if they're, in fact, supplied by the manufacturers, we have no authority to regulate whether they are given to patients. So, that's all voluntary. Sponsors simply make them available either directly to the patients or through the patients' health care providers.

Then there is information that's supplied to pharmacies by independent groups that are not affiliated with drug sponsors. There's currently a large scale

private sector program, in fact, that is driven by specific distribution and information quality goals that's designed to ensure that patients get useful written information about their prescription medicines at the time that they receive their medicines. Now, these are the kinds of things that you generally will see stapled to the bags that people get their prescriptions in. They are computer generated usually at the point of purchase, or at least at the point of dispensing.

Now, there's recent research that we've done that indicates these are fairly widely distributed to patients. So, many patients get this kind of information. However, there's also recent research that suggests that the quality of the information varies considerably, especially in the area of risk disclosure.

Now, this kind of information is out there. It's not required to be given out, but there is a private sector program that encourages that to be given out.

The second type of information that patients receive when they're dispensed certain prescription drugs is mandated by specific regulations for FDA approved patient labeling. These are also known as patient package inserts, or PPIs. Now, the regulations are out there only for certain products, for instance, for oral contraceptives and for estrogen replacement therapy. In this case, the

sponsor drafts the information. The FDA approves the information. Because the regulations are different, there's different format involved, there's different content involved. These, on the other hand, are required to be distributed to patients.

However, there are questions that remain about whether in fact that distribution requirement is being achieved. For instance, some early research that was done with oral contraceptives and whether they were being received by patients, indicated that over 90 percent of patients were getting the information. These are packaged in unit-dose packaging. I'll explain that in a minute. Whereas, another study showed that for estrogen replacement therapy, which is not packaged in unit-of-use, only about two-fifths of the patients were getting that information.

Now, when I say unit of use, what I'm talking about basically is where the product comes kind of automatically packaged in the amount that the patient is generally prescribed. You'll see many topicals and many inhaled medications coming in this kind of packaging so that the pharmacist doesn't have to repackage it. It doesn't go into little amber bottles. They just slap a label on it and give it to the patient. This is basically something that is required in Europe but is not required in the United States.

Now, a second type of FDA approved patient labeling is labeling that is essentially a case where the FDA and the manufacturer agree that patient labeling for the particular product is appropriate. Again, the sponsor drafts it. The FDA approves it. There is absolutely no uniformity in either the format or the content of what goes into the labeling. It really depends on the sponsor and the review division that is reviewing it. Basically it's all over the board. So, there's no consistency, especially in having a uniform format where the patients would be able to find the information specifically that they're looking for.

There is also no clear agreement as to whether this information is required to be distributed, unlike where you have a regulation that says, yes, this is required to be distributed. We certainly have anecdotal evidence that indicates that the actual distribution is spotty, again especially when the information is not packaged in unit-of-use packaging along with the product.

Now, the third type of information that's the focus here is what are called medication guides. Medication guides came into being relatively recently with a rule that we finalized in 1998 and became effective in June of 1999. This is unlike the products that are covered by specific regulations for patient labeling. This rule

was designed to identify products for which patient labeling is critical for safe and effective use. Again, the sponsors draft this information. FDA approves it. It was designed mostly for outpatient products that pose a serious and significant public health concern that the agency believes that the information, as I said, is necessary for safe and effective use.

On average, the agency expected that between 5 and 10 products annually would need this kind of information.

Again, to address the issue of distribution, the rule actually requires that the information be distributed to patients, similar to the oral contraceptive and the estrogen replacement therapy regulations.

When would you need a medication guide? The rule basically specifies three circumstances under which a medication guide would be appropriate for a product. One of the circumstances, the first one, would be where basically the information could help prevent serious adverse effects. This is, for instance, where you have warning signs of particular side effects that can be recognized and, if acted upon promptly, can then be averted or the serious consequences can be minimized.

For instance, say you have a product that causes constipation that can lead to very serious

complications of the constipation. An action can be taken to minimize these complications by, for instance, the patient stopping taking the drug immediately and talking to their doctor. So, this would be one instance where a medication guide would be appropriate.

The second type of trigger circumstance would be when the patient needs to know of serious risks that are relative to the benefits of the product that might affect the patient's decision to use the product or to continue to use the product. So, you have a situation here where, for instance, a drug may cause serious outcomes of some sort or even life-threatening outcomes, but the drug itself is used to treat a condition that in itself is not life-threatening. So, the patient needs to know where they fall in terms of determining whether they want to continue to take this product. So, it's kind of along the lines of an informed consent purpose.

The third triggering circumstance is where the drug is important to health and patient adherence to directions is extremely critical to its effectiveness. So, for example, the drug doesn't work unless it's taken in a certain way, say, on an empty stomach, and then no further ingestion for another 2 hours, and it's critical to the patient's health, and you don't necessarily even know that it's not working until something drastic happens.

So, those are the three circumstances under which a medication guide might be required. In many cases, you end up with a lot of overlap, that you have both 1 and 2, for instance.

Now, getting down to the requirements. If you've required that a medication guide be distributed for a particular product, what's in that medication guide? Well, the regulation specifies that it must be written in nontechnical, understandable language. So, we're saying it has to be understandable to consumers. It can't be promotional in tone or content. It must be scientifically accurate. It has to be consistent with labeling.

Even though it needs to be consistent with labeling, the language does not need to be identical to what's in the professional labeling. In fact, if you think about it, if it was identical to what was in the professional labeling, you'd automatically be going against the fact that it should be written in nontechnical, understandable language for the patients.

Also, the information needs to be specific and comprehensive. This is not information that is kind of vague directions for use without explanations because basically if you don't give people a reason for what they're doing, they generally don't do it. A warning is not effective without having the rational behind it. So,

it needs to be specific and it needs to be comprehensive.

It needs to be at least in 10 point minimum type because we have concerns about especially older patients who are taking a lot of drugs who don't necessarily have the best eyesight, and I have to be able to attest to that because I'm not even that old, and my eyesight is definitely failing.

Legible and clearly presented. We're talking about appropriate use of highlighting techniques. You can use bolding. You can use italics. You can use underlining, anything that makes the important information stand out to the patient.

Basically this is the kind of information that needs to be in the medication guide, and it's under headings that are actually specified in the rule. I haven't given you the headings here because of what I'll tell you in a couple of minutes.

The first information that the patient gets is what is the public health concern that created the need for the medication guide. This is basically in a little section that says, what's the most important information I should know? So, if they read nothing else, that is the information that they get.

They will get also the benefits of treating the disease and some information about the disease.

They will get the information about contraindications and what they should do if any of those apply.

What will be included after that is instructions for proper use.

Following that is specific instructions, things for instance to avoid while you're taking the drug. For instance, if the drug causes photosensitivity, there will be a very, very clear direction there to avoid being out in the sunlight and the reason for it. Also, if the drug interacts with other products, that will be included. The risks to mothers and fetuses, to children, to older patients would be included in this particular section.

Finally, the side effects would be included. Now, not every single side effect from the professional labeling, but the side effects that the patients need to know about will be included.

The thing to keep in mind about medication guides is that distribution is required. The manufacturer is responsible for ensuring distribution of medication guides. There are a couple of ways that it can be done. Either they can provide sufficient numbers of medication guides to the dispensers so that every patient will be able to be given one or they can provide dispensers with the means to produce enough. That could be, for instance,

through computerization.

The distributors are also responsible for passing on medication guides. This is also in the rule. And there needs to be a notation on the container label that there is a medication guide -- this is a notation to the dispenser -- and that this medication guide needs to be given out to the patient.

Then finally, as part of the regulation, the authorized dispenser is required to give these out.

Now, we do allow some flexibility. We have built in some flexibility to the regulation. For instance, the FDA can exempt a sponsor from any of the requirements of a medication guide that are in the regulation except for two, one being consistency with the labeling and the other being the title, specifically "medication guide."

Also, if the prescriber believes there is information in a medication guide that would be deleterious to the patient, then the prescriber can direct the dispenser to withhold the medication guide. However, if the patient says, I would like to have the information on this drug, then the dispenser is required to give it out. So, the patient can override a physician's withholding request.

So, in conclusion, medication guides are for products that pose a serious and significant public health

concern for which patient labeling, patient information that is approved by FDA is necessary for safe and effective use. They provide a uniform format and content to facilitate patients being able to find the information that they need to use the drug safely and effectively, and they are required to be distributed to patients.

Thank you.

DR. BERGFELD: Thank you very much. Dr. Ostrove, before you leave, if I could ask a question or so.

DR. OSTROVE: Sure.

DR. BERGFELD: This has been enacted essentially one year, and what is the FDA's experience with the distribution and the monitoring of the distribution?

DR. OSTROVE: We have very little experience at this point.

One concern, obviously, is going to be distribution and monitoring. There are a couple of ways to look at that. One way is to put in place a compliance program to go out and see whether this is being distributed. Another way to deal with it, of course, is by ensuring that the drug is packaged in unit-of-use, in which case the medication guide is already in there, and prescribers don't generally take out the information if something is in unit-of-use. They just give it to the patient. So that way you're almost assured that the

patient is going to get it. Almost.

DR. BERGFELD: The second question I have is how many drugs does this now apply to?

DR. OSTROVE: Currently this applies to two products.

DR. BERGFELD: And they are?

DR. OSTROVE: One of the products is Lotronex, alosetron, which is used to treat -- I've forgotten what it's used to treat.

VOICES: Irritable bowel syndrome.

DR. OSTROVE: Oh, everybody here knows. This is very good.

(Laughter.)

DR. OSTROVE: It's actually the example I gave with regard to serious complications of constipation.

The other drug is Ziagen, abacavir, which is used in HIV treatment and causes a serious hypersensitivity reaction. If the patient is rechallenged with the product, takes it again after having the hypersensitivity reaction, they can die within hours.

DR. BERGFELD: Now, the third question then and my last question is if there are only two drugs that are now on your current list to have this medication guideline apply to it, are there other drugs, foreseeable in the future, that would have this?

DR. OSTROVE: Yes, there are, but I'm not at liberty to say what they are at this point.

DR. BERGFELD: But you will be unfolding those over time.

DR. OSTROVE: Yes, we will.

DR. BERGFELD: Thank you.

DR. OSTROVE: Thank you.

DR. BERGFELD: Yes, Dr. Branch.

DR. BRANCH: What are the implications within a hospital practice of distribution of this information? Because I've not heard of any mechanisms that have been introduced into hospitals to make sure that the patient has their informed consent or the information for this.

DR. BERGFELD: Is that just a statement of fact, or are you asking for a request of information?

DR. BRANCH: I'm asking. If a patient is an inpatient, is there the same obligation for distribution of information to that patient?

DR. OSTROVE: Generally it was envisioned that medication guides would be primarily for outpatient use, but I think that conceptually, yes, they would be under the same obligation to give that information to the patient. The products for which medication guides have been required by the agency at this point have all been outpatient products.

DR. BERGFELD: Yes, Dr. Greenhill.

DR. GREENHILL: Just a simple question. What is the mechanism for reviewing the applicability of a medication guide to a product? Does it come from the sponsor? Does it come from FDA? Does it come from the public? What is the method or the chain of events that might lead to that being included as part of the review?

DR. OSTROVE: The regulation envisions that the FDA would notify the sponsor in writing of its determination that a medication guide is necessary. Certainly the FDA is always open to hearing from the public. There's the whole citizen petition route, and in fact we have gotten citizen petitions on this matter.

Does that answer your question or was there more to it? I'm sorry.

DR. GREENHILL: Is this a standard part of every review when there's potentially serious adverse events? I don't understand how it might be introduced in the review process.

DR. OSTROVE: Okay. That's a very good question actually, that piece of it as well. This is something that all review divisions have been educated about, and they are aware of the mechanism. So, in doing their reviews, at a relatively early stage, they ought to be looking at whether, in fact, the product, its benefits

and its risks, is one for which one of the triggering circumstances would apply and discuss that. In fact, they would then bring that up to a higher level within the center, and there is a coordinating committee at this point that looks at whether in fact a medication guide is appropriate. So, this is not the kind of rule that simply will be applied haphazardly.

DR. BERGFELD: Seeing no other questions then from the committee, we'll move on to the specifics, the Accutane associated psychiatric events. Roche is going to present. Dr. Russell Ellison is the leader, and he will begin.

DR. ELLISON: Thank you, Dr. Bergfeld and members of the advisory committee and FDA. We're pleased to be able to be here to put the psychiatric events associated with Accutane into perspective.

In February 1998, the product labeling was changed from a listing of adverse events to a bolded warning, which was based on a review of spontaneous reports of psychiatric events with Accutane. Basically we had a signal which had yet to be confirmed.

From February 1998 up to really now, Roche has been very diligent in trying to evaluate and trying to confirm this signal. We had a pharmacoepidemiological analysis of reports conducted by Dr. Robert Nelson, who

will present this to you, which is to put the individual reports into the context of science and medicine.

We had a clinical review of reports of suicides and related events conducted by Dr. Jacobs because this does need a special clinical rigor in evaluating these cases.

We also conducted two retrospective epidemiological cohort studies in two very large databases which are very often used to evaluate safety signals, the Uk General Practice Research Database and the Saskatchewan database.

Finally, in parallel with this, we re-reviewed the biological and clinical literature.

We believe that the evidence from these investigations does not support a causal association between Accutane and psychiatric events, including suicide. That is, the signal has not been confirmed by these investigations.

We also believe that these investigations have revealed and shone a light on the fact that patients with acne, depending on age, gender, and prior history, come from a cohort that may be at high risk for concomitant psychiatric illness. We believe that this has led to the opportunities to improve the overall medical impact of dermatologic practice.

After my introduction, Dr. Jacobs will review the clinical context overall for the evaluation of psychiatric events and Accutane. Dr. Nelson will review with us his pharmacoepidemiological evaluation of spontaneous reports. Dr. Jack McLane, our Director of Medical Science and Safety, will review the epidemiological studies and the biological issues associated with this, and I will follow up with a brief discussion of risk management options.

Thank you. Dr. Jacobs?

DR. JACOBS: Good morning, members of the advisory committee and the FDA. I'm a psychiatrist and suicidologist. I have been studying the problem of suicide since 1972 when my very first patient attempted suicide in a hospital by hanging himself, only to be saved by another patient.

My work has included using principles of a psychological autopsy in reviewing over 300 suicides on an intensive basis. I've also developed National Depression Screening Day, which is the first ever national program for screening for mental disorders.

I will first present a clinical context for understanding the psychiatric conditions presented in the MedWatch reports, specifically suicide and depression, first in the general population, then in the major Accutane

population, ages 15 to 24.

I will then discuss the dual use of the term "depression" as an illness versus depression as a symptom, particularly as it applies to medications.

Dr. Nelson will then present an epidemiologic analysis.

I will then return with a clinical analysis of the suicide reports using principles of a psychological autopsy.

In terms of suicide, I'll provide an overview of the clinical and demographic correlates, the clinical features of suicide, suicidal behavior, as it relates to the spontaneous reports, addressing some of the definitional issues, then talk about depression illness versus symptoms, depression's relationship to suicide, and then go into depression/suicide in the Accutane population addressing the epidemiologic risk factors and the diagnostic issues.

In understanding suicide, it is important to understand that it is a multifactorial event. No one factor causes suicide. Over 90 percent of persons who commit suicide are reported to have a major psychiatric illness. 70 percent have comorbidity, particularly with substance abuse.

The factors that go into suicide include:

severe medical illness; personality traits; access to weapons; features of hopelessness; the relevance of family history not just from an environmental standpoint, but also from a genetic standpoint; life stressors; suicidal behavior, its relevance, impulsiveness; and neurobiology.

In terms of Accutane, I've examined from a clinical perspective, psychiatric illness, neurobiology, impulsiveness, and suicidal behavior.

You see up here in the corner, I have "no apparent psychopathology." This is particularly important for understanding the MedWatch reports, specifically in young people. I will address that further when I talk about suicide in young people.

This is U.S. data. The incidence of suicide has remained about the same for the past 10 years. We have seen a slight drop, but the basic incidence is that there are about 30,000 suicides per year. 80 percent of suicides are in males, and it is the third leading cause of death in young people, representing 20 percent of suicides, approximately 6,000 per year.

In terms of the clinical features of suicide, suicide is associated with severe depression. The majority are not in mental health treatment. 75 percent have seen a physician in the previous six months. As I mentioned earlier, no one factor is predictive of suicide. 60

percent of persons suicide on the first attempt, and no medication has ever been proven to cause suicide.

If we apply these two areas to the profiles of suicides in the Accutane reports, we see that 80 percent of the suicides were in males. The majority were not in mental health treatment. 75 percent had seen a physician in the previous six months, and the suicides that occurred were primarily on the first attempts.

In terms of suicidal behavior, suicidal ideation, which again is listed in many of the reports -- and there are two primary definitions. There is the non-specific, which includes thoughts of death, and then the specific, which is the more serious and how we look at suicidal ideation. That's not only the thought of death, but it's the thought of death accompanied by an intent to die with a plan.

The prevalence of suicidal ideation is about 2.6 percent, and that's from NIMH data.

Thoughts of death, which occurs approximately in 28 percent of the population, obviously is 10 times the incidence and, in my view, appears a lot in the case reports.

Suicide attempts. Much more difficult to study. The basic distinction is self-destructive behavior that is accompanied by suicide intent versus self-

destructive behavior that is reported regardless of intent to die. This has particular relevance in the young population. In the general population, there are reported to be approximately 18 to 1 in terms of attempts per completion. In the young population, anywhere from 100 attempts to 1 completion. Many more self-destructive behaviors, the intent much more difficult to establish.

In trying to put suicidal behavior into some perspective in terms of suicide completers, we believe that there are approximately 5 million people who have serious suicidal ideation. The majority do not go on to attempt suicide, and a very small group, less than .6 percent of people who experience suicidal ideation go on to complete suicide.

Depression is a prevalent disorder. Approximately 12 percent. Again, these are U.S. figures. Approaching about 20 million people. Depression is under-diagnosed and under-treated. Only 20 percent of persons with a recent episode get treatment; 40 percent lifetime. 20 percent of persons with depression appear in general medical practices, 50 percent of whom are undiagnosed. Therefore, in terms of the MedWatch reports, it would not be unusual for a person to be either currently depressed or in the beginning of a depression and appear in a dermatologist's office.

There has been a decreased age of onset since World War II, and the male/female ratio is 1 to 2.

It is important again, in understanding the MedWatch reports, to understand the distinction between depression as an illness versus depression referring to depressive symptoms, "the blues." When we talk about depression, we're talking about an illness, a syndrome. In the DSM-IV, it is five of nine criteria. There's severe social impairment. The symptoms have to last for two weeks or more. It is an episodic and persistent illness. The symptoms not only have mood, loss of interest, biologic symptoms, including sleep, energy, appetite, but cognitive symptoms, including feelings of worthlessness, drop in self-esteem, and the most serious, thoughts of death and suicide.

Whereas, with the blues, which are a normal reaction to life events, the prevalence is twice as much, about 25 percent. The symptoms are singular, usually affecting mood. They're temporary. They rarely produce suicidal thoughts and usually time will heal or a good listener, where the illness of depression requires medical and psychiatric treatment.

The issues of medication and depression. I put depression in quotes because again we're dealing with the dual use of the term. The question, are medications that

are reported to cause depression, which are approximately 100, associated with diagnosed depressive disorders or depressive symptoms?

The majority of medications that are reported in the literature come from case reports. When there have been attempts to look at these medications from empirical evidence, the reports are inconclusive. Beta-blockers are the major example. There have been multiple case reports of beta-blockers "causing depression." When one looks at the literature, the literature is inconclusive and, in fact, states that they are not associated with clinical depression. If they're associated with anything, they're associated with depressive symptoms. The clinical significance of depressive symptoms is minimal.

Adolescent depression. Dr. Nelson will talk about the prevalence, but to state that adolescent depression is a prevalent disorder, its features make it particularly difficult to diagnose, including increased moodiness, irritability, argumentativeness, increased self-criticism, increased talk of death and dying, and threats of suicide. Normal adolescents often appear moody, frequently argue. The symptoms of depression overlap with traits of normal adolescents. Parents, teachers, and other adults label it troubled teenage behavior.

I've bolded this last item because this again

is relevant to the MedWatch reports. Adolescents conceal symptoms from parents and caregivers, which makes it particularly difficult in understanding depression and specifically suicide.

In terms of the relationship to stressful events, depression can occur in adolescents and in adults 50 percent of the time with a stressful event, 50 percent of the time without.

Here's a chart that looks at the suicide rate for all persons compared with the suicide rate for persons aged 15 to 24 from 1900 to 1995. I've highlighted 1950 and 1980 because since 1950, from 1950 to 1980, the suicide rate has tripled in the young population, ages 15 to 24, from 4 per 100,000 to 12 per 100,000. As of 1995, unfortunately, the suicide rate in young people has exceeded the suicide rate in the general population.

In applying the model that I showed earlier to adolescents, there are specific issues. If we look at the age-specific stressors, that is where severe acne comes in in terms of its impact on self-esteem, but other issues in young people are academic problems and the role of a disciplinary crisis and humiliation. But in order to understand suicide in young people, we have to look at exposure to suicide, conduct disorder, access to weapons.

Now, again, no apparent psychopathology. We

believe that about 5 to 10 percent of young people on the surface, when one hears about a suicide, there is no apparent psychopathology. It is not uncommon to read newspaper stories where the suicide occurred out of the blue.

But if one conducts a psychological autopsy and looks at these suicides, we see that there was subsyndromal psychopathology. There was a past history of suicidality. There was a familial psychiatric disorder. There were legal/disciplinary problems, and there was presence of a firearm. The important point here is that one cannot understand these particular suicides unless one conducts a psychological autopsy.

I will now turn the podium over to Dr. Nelson who will present an epidemiologic analysis and then I will return with my suicide review.

DR. NELSON: Thank you, Dr. Jacobs. Madam Chairman, committee members, Dr. Woodcock, and former FDA colleagues, good morning. I'm pleased to be here to discuss this important issue.

Over the 18 years of Accutane marketing, there have been many reports received through spontaneous reporting systems, which describe psychiatric symptoms or disorders in temporal relationship to the administration of Accutane in patients with severe acne. Reviews of these

issues were conducted in the past, and the current labeling reflects the most recent understanding of the regulators.

Last year I was commissioned by Roche to review these reports as a pharmacoepidemiologist. My full report was submitted to the agency earlier in this year, and a copy of the main body of the report, without its 20 appendixes, is included in the materials that the committee received as appendix 13. By nature and necessity, this presentation will skim over most of the analyzed data and detail contained in the full report.

This is the presentation overview. I'll follow this format.

The objectives are to determine the nature and the extent of any relationship between Accutane therapy and psychiatric morbidity, to describe the types of reported psychiatric disorders, identify all associated risk factors, assess the magnitude of those identified risk factors, and to evaluate causality within a pharmacoepidemiologic framework.

The overall method of risk definition, when utilizing observational data from these spontaneous reporting schemes, is to identify a signal, attempt to confirm that signal in external databases, then if confirmed, strive to quantitate that confirmed risk. Unlike an experimental setting, these three steps require

different logic and the use of different data sources for their proper execution.

The methodology I used is on this slide. An extensive literature review, of course, was an important component of this review. This is a complex area, as Dr. Jacobs showed you in his multifactorial slide. Over 250 citations were used in this report, extensive review of the etiology and epidemiology of psychiatric conditions, including suicidal behavior. And I tried to conceptualize and propose the interrelationships between the various factors in this model.

I reviewed the spontaneous reports to evaluate them for category, quality, and content, and to determine the value of spontaneous reports in explaining the proposed relationships that were developed during the literature review.

Then I reviewed the epidemiology and conducted some epidemiological analyses to evaluate the relative likelihood of all the risk factors identified and to derive the relevant conclusions.

Dr. Jacobs already provided a summary of the literature review that's in the report, so I'll move right on to the spontaneous report review.

Spontaneous reporting systems were designed 35 years ago to identify new, unusual, serious, and rare

reactions. These reports are anecdotal, and when they are from health professionals -- and not all of them are -- they are an index of suspicion of clinical observation.

In the United States, most of these reports are received first by the manufacturer and placed into a corporate database by something known as the reporter term. That's an extraction of the verbatim language in the reports and matched to a coding dictionary to file it away in a database. Roche uses the coding dictionary of WHO-ART currently. So, what I did in my review is look at all the psychiatric cases within the WHO-ART system organ class, which included every report that Roche had in their database.

It's important to understand that these reporter terms are filing terms and not necessarily analytical terms. To understand this concept of the reporter term is key because if the reporter is a physician or a parent, the verbatim language is used. For example, if a physician calls a particular episode "major depressive disorder" that gets coded as depression. If a parent says my son was depressed, that also gets coded as depression.

I took the reports in the Roche database and I organized them by the eight functional categories outlined in the DSM-IV. I reviewed each and every report that was received by Roche between 1982 and a data lock point of

April 30, 1999, and I reviewed all the reports worldwide, not just those in the United States.

Reports of psychiatric events represent approximately 9 percent of all the reports received for Accutane, and the vast majority of these reports were, as you can see here, for mood disorders or symptoms. 53 percent fell under the collective DSM-IV umbrella of mood disorders. Now, because I put them under there, doesn't mean that they were all mood disorders. They were descriptions, whether they be symptoms or diagnoses that fit under that general umbrella for categorization purposes.

We focused in the review on mood disorders, psychotic disorders, and suicidal behaviors because those are the three entities that are in the current labeling. The details of the terms I excluded are in the report.

Now, when you try to assess the relationship between a drug and an adverse event, there are eight reasons that you go through intellectually to sort them out.

The first, obviously, is the temporal association.

You then look to see if there's a dose-response event occurring in these cases.

You look for a dechallenge. That is, if the

drug is removed, do the symptoms abate? You look for rechallenge. If the symptoms have abated and you reintroduce the drug, do the symptoms come back? When you have a positive dechallenge and a positive rechallenge in a spontaneous report, that is usually considered your strongest evidence of a causal association.

You also look to see if there's a mechanism of action that's known and understood and plausible. Although biological plausibility is not necessary, it is helpful to have one.

You look at class effects. Are there other drugs in this pharmacological class that have reports or hopefully better evidence for a causal relationship?

Then, of course, you look for alternative explanations. If you have no reasonable alternative explanations and many of the items on this chart, you have a very good case for causality.

So, you look at the individual reports. You assess their coded reporter term. You assess the quality of the data, consistency of the data, including all the data elements, including things like onset and offset. You relate the reports to the seven reasons I had on the prior slide. You group like reports and you review them as a case series for content and consistency, and then you make your causal assessments.

This is a very important slide to understand. When spontaneous reports are well-documented and for rare adverse reactions that have background rates that are low, spontaneous reports yield their most defensible data. Spontaneous reports are of very diminished value when the outcome has a common background rate. Spontaneous reports can be a very powerful tool. However, they can also be misunderstood and abused as a tool. Spontaneous reporting was never intended and cannot be used as a quantitative tool and has little interpretative value when the natural history of the outcome is common.

Again, I reviewed and analyzed and evaluated all the reports, and there are 100-plus pages of detailed analysis in the submission. Having said that, I'm going to go right to the results of what I found.

There were 1,247 total reports under the DSM-IV domain of mood disorder. Of those reports, there were 367 that had a dechallenge that was positive. What I'm trying to do here is boil down and find the best cases amongst them. Of that 367, I identified 23 cases that had both a positive dechallenge and a positive rechallenge. As I defined before, these are the best cases. 37 of that 367 had a diagnosis for a mood disorder subsequent to the exposure. The rest of them did not have a diagnosis, and I used that term very conservatively. Whether a physician

reported a diagnosis or whether a treatment was given, I considered that a diagnosis.

Most of these cases, especially the 23 here, are very strong, and I'm sure that the clinician that reported them was convinced that these were a cause-and-effect relationship, and when you review them at the individual case level, that's your conclusion.

What I want to show here, because subsequent to the report, FDA had given us a list of additional reports that they considered to fall in this category, so we created a master list of the original 23 and the unique ones that FDA had sent. Some of the differences accounted for -- some of them came indirectly to FDA through the MedWatch. They also used a one-year-later data lock point. So, that explains some of them, and the other ones were just a difference in judgment because, again, this is an interpretation of a spontaneous report.

I make this slide just again to illustrate the point that while most of them are from health professionals, only 4 out of the 34 cases had a formal diagnosis. The rest were most likely reports of just symptoms.

Without going into detail, I'll tell you -- and you'll hear a little bit about it this afternoon -- that these dechallenge and rechallenge cases, both levels, have

tremendous amount of diversity and inconsistency. I could find no pattern of data within them.

So, what my summary is from the review of the individual cases is that at the individual case level, a small number -- and whether that's 23, 34, or 41 -- you'll hear different numbers this afternoon -- the conclusion is the same. At the individual case level, a small number of cases imply a causal association between depressive symptoms and/or mood disorders and Accutane. This conclusion is consistent with the reviews you'll hear from FDA this afternoon.

Psychotic disorder results. I'm going to go through this a lot briefer. There were 120 total reports under the DSM-IV domain of psychotic disorder. 20 of those had a dechallenge. 5 had a positive rechallenge and dechallenge. 3 of the 20 had a diagnosis. Of the other reports of lesser quality, there were 9 additional diagnoses, for a total of 12 diagnosed cases out of the 120. When I reviewed each of them in a case series, I can find no consistency on any of the parameters.

So, my conclusion from a review of these reports is that, again at the individual case level, there are at least 3 -- at least 3 -- that imply a causal association between the described psychotic disorder and Accutane administration.

Suicidal behavior reports. Here I've included both suicide attempts and completed suicides. Suicidal ideation is under DSM-IV as a depressive case.

There were a total -- and this is worldwide total -- of 168 reports before the data lock point. 104 were attempts; 64 were completed suicides.

Overall, the suicide reports were poorly documented, and none had anything close to a psychological autopsy performed. I could find no relationship amongst the data in these reports and no dose relationship. The male/female ratio is 5 to 1 for the completed suicide reports. The ratio is quite different for the attempts.

In summary, I could find none of these 168 reports that imply a direct causality. Let me explain to you a minute what I mean by direct causality. It means that it does not include an intermediate stage of a psychiatric disorder. So, none of them implies a direct causality between suicidal behavior and Accutane administration at the individual case level.

Dr. Jacobs will come back in a few minutes to go into those cases in detail, as he said before.

What I'm going to do now is go into the epidemiology and the epidemiological analysis. What I need to do is set the stage a little bit over the next few slides. I'm going to focus in on the age group 15 to 24.

That's the modal age group. That's where about 70 percent of the Accutane users are, including 85 percent of the males and 55 percent of the females. I'm going to focus in on that group because that's where my comparator data are and I want to have like cohorts for those comparisons because I'm going to assess these cases in light of the natural history of the disease.

From the National Comorbidity Study here in the United States, I will take the 1-year prevalence, 12-month prevalence, of major depressive disorder and use that in my analysis. Now, I'm going to be very conservative. From here on in, I'm going to use major depressive disorder. I'm not talking about the symptoms. I'm going to focus down for comparisons on both the case level and the natural history level on major depressive disorder. Very conservative.

Again, these data are from the National Comorbidity Study which is considered the best epidemiological study on psychiatric morbidity. These are U.S. data only at this point because that's a U.S. study.

Notice the male to female ratio of 1 to 2.

I need to set up the slide for you because this is very important to my argument. We take the cohort of Accutane exposed individuals in the United States. Roche has estimated that to be, at the time of this study, 3.2

million individuals. I take 70 percent of that to create a cohort of 2.5 million individuals in this age group that have received Accutane over the last 18 years.

The specific calculations for all these charts are on page 42 of my submission in appendix 13, if you have any specific questions about how I got these numbers and what calculations I used.

If at time 1 you have a 2.5 million person cohort that has not yet received Accutane, what would you expect as far as psychiatric morbidity related to major depressive disorder only at that time? What you would expect, based on the epidemiological evidence, is 152,000 individuals with current active major depressive disorder. You would expect an additional 240,000 individuals of that 2.5 million cohort to have a history of major depressive disorder but not actively symptomatic at time 1. The vast majority of the individuals have no history and no active disease, 2.1 million.

I'm going to take these three sub-cohorts and pass them through a 6-month exposure to Accutane. I know that most of them get it 4 months. We used 6 months to have a good comparator. What happens? Of the 152,000 with current disease, no change. In other words, disease will go the entire 6-month period in about 30,000, 20 percent. You would expect 80 percent of those cases, since

depression is a cyclical disease, to abate. But 35 percent of those that have already abated would have reoccurred in that 6-month time period, to give you an additional number of 42,700 at time 2.

Of those with a history of disease, but no active disease at time 1, passed them through the 6 months, and you would expect again a 35 percent reoccurrence of disease, to give an incidence of reemergence of symptoms here of 84,000 from this subgroup.

Of the 2.1 million that have no history and no active disease, using an incidence rate of 1.2 percent, you would expect a true incidence of 25,290 to have occurred first time within that 6 months. These are amazing numbers.

You add these together, and at time 2 you have a prevalence of 182,500 with a total incidence -- new incidence, plus all reoccurrence of disease -- of 152,000 cases. That means that during the 6-month period of exposure to Accutane for these 2.5 million individuals, 152,000 had a reemergence of major depressive disorder.

Now, how does that relate to the cases? If you take the new incidence of 25,000 and contrast it to the newly diagnosed cases in the database -- and again, the 102 is going to be very conservative. When in doubt, I put it in -- you get at most 102. When you contrast the total

incidence of 152,000 to all the cases in the database that could be considered new incidence or reoccurrence, this is the contrasting figures. These are the cases, the vast majority of them which were not, by any stretch, a diagnosable disease. They were symptoms.

Now, take the 152,000 and let's populate a scatter plot where you have the y axis being the quantity of cases, the x axis being time to onset or offset or re-onset or re-offset, and then the z axis, the dose. This is an illustration. This is not data-driven. This is an illustration. Please understand that because we don't have the data on 152,000. But it's an illustration to prove the point that on a dose duration matrix, every one of the possible data points have hundreds, if not thousands, of cases that can explain what you see on clinical observation regarding onset, offset, or rechallenge.

So, every onset and offset -- in other words, a positive dechallenge or positive rechallenge seen in the spontaneous reports -- could be accounted for by hundreds of background cases of this cyclical disease. Therefore, given this extreme density, it is difficult to value even the most rigorous individual case report. It is very easy to be misled by coincident individual clinical observation here.

In addition to that very high background rate

of disease and even higher background rate of symptoms, there are a number of very substantial risk factors that need to be taken into consideration in this population. These data that I'll present now are again U.S. data from the U.S. Substance Abuse and Mental Health Administration's National Household Survey.

For this age group -- and we're still talking here U.S. -- that survey estimates that 7.2 percent of these individuals will be heavy alcohol users. That's defined in the survey as 5 or more ounces of alcohol 5 or more times a month, substantial alcohol consumption. That's a cohort of about 180,000 from the 2.5 million. Approximately the same number will be illicit drug users.

Assuming extensive comorbidity, combined alcohol and drug abuse, you can estimate that to be about a quarter of a million or about 10 percent of the total exposed cohort of young Accutane patients would be expected to either be a heavy alcohol user or a substance abuser or both.

So, you put these alternative risk factors together and you have a quarter of a million alcohol/drug abusers amongst that cohort. Many of these abusers, of course, are comorbid with the 152,000 incident cases of mood disorder. So, you have a total number of persons in this cohort with some form of DSM-IV disorder that could be

up to 20 percent or one-half million individuals.

Psychotic disorders. I'm going to do this one real quick. You would expect in that cohort that we've been examining a prevalence of about 1 percent, possibly less. A male/female ratio, unlike depression, is 1 to 1. These are basically schizophrenic patients, but given the amount of exposure, you would expect about 25,000 cases, prevalence.

In the older group, you have more prevalance. This is a figure with the age and gender adjusted distribution of Accutane users. You would expect an additional 14,000. If you add the covariates of alcohol/drug abuse and age and gender adjust them, you would get an additional 4,000. Assuming some comorbidity, of course, you can estimate that of that 2.5 million person cohort, you would have expected 40,000 prevalent cases of psychotic disorder. We had in the case reports, 120 case reports, 12 of which were diagnosis.

Suicidal behavior. My first chart here is from a reference by Beautrais, et al. in 1996. I put it up to show you some empirical data. These are suicide attempts and the relationship of psychiatric disorders to suicide attempts. This is just for females, this part of the chart, under 30, over 30. You'll see odds ratios here ranging from 21 to 58, depending on age of the female for

mood disorder. That's interpreted if you have a mood disorder, you are 21 to 58 times more likely to have a suicide attempt than if you did not have a mood disorder. That's an attributable risk of about 80 percent, and it's brought up here to show that -- and then you add the other psychiatric conditions. Suicidal behavior without depression or psychiatric morbidity is rare.

Take the cases that were in the database and compare them to their comparable national estimates. There were 64 cases in the database. I take the 38 that were from the United States for this analysis. All I've done here is take the death data from the National Center for Health Statistics, 1997 mortality data, and I age and gender adjusted them and spread them along the bottom part of this chart and called them "expected suicides," and then took the cases in the database, the 38 U.S. cases, and put them across age and gender on the top.

If you didn't know the context, you would see 38 cases and you would comment that that possibly is an excessive amount. What you see is you expect nearly 400 cases in that cohort of individuals. Suicide is rare but it does occur. So, there's no excess in the reports in the database, and you can see the gender and age distribution to be very representative of what would be expected. My conclusion by looking at these case reports and looking at

these kinds of data is that it's very likely that these reports are a sample of what would be expected.

Conclusions. There are a small number of reported cases that imply causality between depressive symptoms or mood disorders and Accutane administration at the individual case level. There's no question there's a signal.

However, an assessment in the context of natural history and alternative risk factors provides strong evidence that the described symptomatology and disorders are much more likely to be associated with factors other than Accutane. So, I failed to confirm that signal.

Unfortunately, analysis with these kinds of data do not allow any potential risk factor to be completely ruled out no matter how unlikely it may appear.

My conclusions for psychotic disorders. Again, there are a very small number of reported cases that imply causality between the described psychotic disorder and Accutane administration at the individual case level. However, an assessment in the context of natural history and alternative risk factors provides strong evidence that the described symptomatology and the disorders are much more likely to be associated with factors other than Accutane. Unfortunately again, these type of data do not

allow any potential risk factor to be completely ruled out no matter how unlikely it will appear.

Conclusions for suicide. There are no reports amongst these 168 reviewed that imply a direct causal relationship between the administration of Accutane and suicide or suicidal behavior. An assessment in the context of the natural history and alternative risk factors provides strong supporting evidence -- the evidence is not as strong as in depression -- that the reported cases are much more likely to be due to the factors other than Accutane.

Dr. Jacobs will return in a minute to give you a detailed clinical evaluation of these cases because that's where the real strength lies.

My overall conclusions. Given no clear biological plausibility, no consistent pattern in the data that I reviewed, complex environment of background symptoms, very high background rates of disease, very high background rates of alternative risk factors, I conclude that there is no evidence in these data to support a causal relationship between Accutane administration and psychiatric disorders.

Thank you very much for allowing me the opportunity to place these data into proper perspective.

Dr. Jacobs?

DR. JACOBS: While I was here, I did want to specifically answer your question you asked yesterday, Dr. Malone, about Accutane and CNS. There's no scientific evidence that Accutane affects the neurotransmitters at all, and Dr. McLane will address the issue of biological plausibility after I'm finished.

What I've done in my clinical analysis of the suicide reports is I asked the following questions. Is there any pattern to the suicide reports in relationship to Accutane in terms of gender distribution, in terms of on/off Accutane? What is the significance of the temporal association with "depression"? Does Accutane exacerbate underlying psychopathology and lead to suicide? As you'll hear later on this morning, there were a number of suicide reports which had preexisting psychiatric illness. Does Accutane cause impulsive suicides?

I broke the suicides down into various categories in terms of their relationship to Accutane use, the concealment of symptoms, which I mentioned earlier in terms of the youth suicides, the confounding factors, the preexisting psychiatric history, the issue of no apparent psychopathology, and miscellaneous.

In terms of the relationship to on/off Accutane, there were 30 cases on Accutane, including 4 that were on over 6 months, 24 cases off, 10 unknown. No

evidence of a predominance of on/off factor. In terms of gender -- and these are worldwide. These are not just the U.S. cases -- of the 64, 53 were male, 11 female. The total suicides, as mentioned earlier, are consistent with the known demographics of suicide. In looking at the on/off ratio, again the gender distribution is the same.

Further, some case examples of relationship to Accutane. There's a case described of a 22-year-old male, no relevant findings. Committed suicide by firearm. I should mention that these are typical of a lot of the suicide reports. There's very little information. But if we compare this with a 19-year-old male who committed suicide, the same method, had a preexisting history of psychosis, there's evidence of school stressors, and was on Accutane for 6 months. While he's on, there's no evidence of exacerbation of his underlying illness. He commits suicide 9 months later. My analysis, no consistent relationship to Accutane, if you compare these cases.

Depression occurring while on Accutane. 17 out of the 64 reports indicate "depression." 10 of the cases committed suicide on Accutane, 7 off, and only 1 case had psychiatric treatment. Again, no consistent relationship with the term "depression."

What about concealment of symptoms? And there are a number of cases unfortunately like this. This is a

case of a young boy, 14, who was on Accutane for 2 months. No reported psychiatric history. No evidence of depression or suicidal ideation while he was on Accutane. However, there is evidence of preexisting depression and suicidal ideation. This was discovered by a diary after the suicide. Depression with suicidal ideation requires psychiatric treatment. Therefore, the depression and suicidal ideation was concealed from family and physician.

Prior psychiatric history related to on/off Accutane. In my view, this is very compelling information about the Accutane story and suicide. What is the impact of Accutane on this at-risk group for exacerbation of underlying illness leading to suicide? There were 21 cases that I could find that had preexisting psychiatric history. 9 committed suicide on Accutane, 12 off.

What I did is I looked at the cases off of Accutane. One could think about it, in a sense, as a controlled case. These were patients who were at risk. They did commit suicide. Obviously, they were given Accutane. One could not do a study like this.

The duration that they were on Accutane varied from 3 months to 18 months. In terms of the time off, it's anywhere from 6 months to 10 years. While these persons, again at risk, were on Accutane, they did not develop symptoms of their underlying illness. Accutane did not

precipitate symptoms. The suicide, therefore, was unrelated to Accutane and was clearly related to the underlying psychiatric disorder.

A case of no apparent psychopathology. Here's an 18-year-old male, was on Accutane less than a month, no history of depression, mood swings or stressors. He committed suicide by inhaling pellets placed in a canister attached to tubing and a face mask. If one analyzes this, certainly this is risky behavior. The method was suggestive of getting high, and then there's a whole question here about the suicide intent and was this an accidental death.

These are some miscellaneous cases. This is a tragic case of a murder/suicide, of a woman who was on Accutane for 8 months and was off it for 4 months. At the end of that 4-month period, she killed herself and her child by drowning. The child had not been exposed to Accutane. There was a prior history of postpartum depression. The Accutane was stopped because of "delirium," hospitalization offered but refused.

In analyzing this case, infanticide is consistent with psychotic depression. Postpartum depression occurs in manic-depressive illness. The delirium described was most likely a psychotic episode. The events here were related to a severe underlying

psychiatric disorder.

In terms of impulsive behavior, here's a case of a 21-year-old male with a psychiatric history. The patient had been in and out of substance abuse rehabilitation treatment. Was on Accutane for 6 months. During that period of time, there was no report of depressive symptoms nor of drug relapse. He committed suicide 1 year off of Accutane.

In terms of my analysis, substance abusers are at risk for mood disorders and impulsive behavior. Accutane did not cause relapse of any of these symptoms. Therefore, the suicide was related to the preexisting psychiatric condition and happened a considerable amount of time after the discontinuation of Accutane.

In summary, there's no alteration of the gender distribution in the suicide cases. There's no impact of on/off Accutane. There's no significant relationship to concurrent depression. There's no exacerbation of underlying psychiatric disorders. The lack of warning signs seen in many of the cases is consistent with what we know about youth suicide, and there's no evidence of a impulsive factor.

Thank you. I will now turn the podium over to Dr. McLane.

DR. McLANE: This is where we are in the series

of talks. I'm going to present a couple of different types of analyses in order to confirm the signal.

When we look at the material that we have, Dr. Jacobs and Dr. Nelson have looked at the post-approval analysis. They've looked at the spontaneous reports and have done this type of analysis. We had also initiated, when we started looking at the signal, a series of epidemiological studies. One of them was to look at the relative risk. Another was to look at the prescribing behavior. I'm going to show, very quickly, the results of this information.

We've also gone in and looked at the prospective analysis, using our clinical trial that we were running with a new formulation, to see what type of information we could obtain on patients that were being treated with Accutane at different doses.

The first analysis was a retrospective epidemiological analysis. The purpose of it was to determine the relative risk for psychiatric disorders. This was a population based epidemiological study with matched control cohorts. It involved an analysis of the prevalance rates for a variety of psychiatric disorders and suicide and suicide attempts. There were not sufficient numbers in the suicide and suicide attempts in order to do an analysis.

It also brings up that there were a number of caveats within this type of study. These have been presented in your briefing document and will be presented later this morning. But it involves the types of codes that you can use for ascertainment of the psychiatric conditions, the actual type of acne the patients had, the history of the patients, and also even the power. These types of studies are at best just supportive.

The two different types of databases that we looked at within this are the Saskatchewan Health Database in which we were able to identify, using the definitions within the study, 7,000 Accutane users, and we compared this with antibiotic drug users in which we were able to identify 13,000 patients.

The smaller study, which I won't present any results from, was the United Kingdom General Practice Research Database, in which we had only 340 Accutane users and 676 antibiotic users.

Let me just show you the end results. When we compare the relative risk for developing of psychiatric conditions compared to non-exposed Accutane patients -- these are the Accutane patients that were, by definition, prior to their exposure to Accutane -- you see that the relative risk was 1.

When you compare it with patients 3 months

after their first prescription for Accutane, you also see that the relative risk was quite low, and basically the relative risk of 1 means that it was exactly the same as your comparison group.

When we looked at the antibiotics, you also see that the relative risk was very low. The confidence intervals were wide enough to say that this was near unity.

When we looked at the history of the patients that had development of psychiatric conditions, as expected, we saw that the psychiatric history was the only predictive factor for development further of additional psychiatric conditions.

Another way to look at the information was to use other epidemiological tools. There's a new tool that's been developed by Dr. Hallas and was published in the Journal of Epidemiology in which patients are evaluated for the prescriptions that they receive before a drug of interest versus prescriptions of antidepressants they receive after the drug of interest. So, we looked at this information. In the publication, this was used to confirm a signal for ACE inhibitors and for calcium channel blockers. In order to look at the signal, what you do is you develop a prescription sequence ratio. You're looking at the symmetry analysis of this prescription. So, in our case, we were looking at the number of patients that were

prescribed Accutane before their antidepressants, and you develop a ratio with the number of patients that were prescribed Accutane after the antidepressants. A ratio near unity indicated no effect.

We also looked at this by relationship to all antidepressants, amines, the SSRIs, or other ones that were identified. The database that we looked at was the Synergy Pharmacy Claims Database. This database covers 30 percent and registers 30 percent of all prescriptions in the United States. So, it's a very large database in which we were able to identify 17,000 Accutane patients within this. However, for the prescription of having a co-medication for antidepressants as well as Accutane, we were able to get this type of ratio. So, for all of the antidepressants, we had 1,300 versus 1,400 patients before and afterwards, and from that adjusted rate ratio, then we were able to see that this was near unity.

If this was non-symmetrical, as it was with the ACE inhibitors, the adjusted rate ratio for ACE inhibitors was 1.29. For calcium channel blockers, it was actually 1.31. So, again, this is information that provides evidence against an association of Accutane use with antidepressants.

We looked at this for comparison purposes for minocycline. Minocycline in this age population is used

predominantly for acne. Again, we see the same type of near unity for the antidepressant prescriptions that are prescribed before and after the use of the minocycline. This report will be submitted to the FDA. We just received it in the last few weeks.

Another way to evaluate this is to look at the prospective analysis of the signal. In order to do that, we were able to use two tools within our study. The first was a mood assessment questionnaire. This is four questions that we asked at every monthly visit of the patients. If the patient had two positive answers to these four questions -- these questions were developed by Dr. Jacobs and are just typical mood assessment questionnaires on sleeplessness, how they feel, and so on since their last visit. If they had two or more positive answers in there, they were then asked to take the Beck's Depression Inventory at that visit.

In addition, the Beck's Depression Inventory was used for every patient at the beginning of the therapy, at baseline, and at the end of therapy, which was at 20 weeks in this trial.

The Beck's Depression Inventory is a very useful tool in order to measure sensitivity of changes from one category of depression to another. So, it was an appropriate tool to use. It's also been a tool that has

also been used to confirm other signals for drugs that have caused antidepressive effects.

The change of the scores that we were able to obtain within the trial showed that with the new formulation -- which the patients were exposed just once per day at .4 milligrams. They had 250 times less exposure than the patients being treated with Accutane. So, this also allowed us to evaluate a dose effect in this trial as well.

What we see is that the majority of the patients did not change categories. Here we're looking at just the categories which is the Beck Depression Inventory, which is minimal, which is 0 to 13, mild, moderate, or severe. We had no patients that were severe. And we're looking at the change in that category or the change in grade. You can see that the majority had no change in their grade or score. However, there were some patients that had a decrease in their grade, going from moderate to mild or mild to minimum or even moderate to minimal. This would be the change of a grade of 2. We had a few patients that also had a change in grade going from minimal to mild or mild to moderate. There was a very good balance between the two different formulations, as well as the balance between change in grade upwards versus a change in grade downwards. In fact, there was the trend of going

downwards.

When we looked specifically at the mean scores of the Beck's Depression Inventory, then what we find is that on the baseline levels on both of the arms of the trial, we had 3.5 versus 3.6, and at week 20 at the end of their successful therapy, we had a mean Beck's Depression score of 1.7 and 1.9.

It's been known, for example, that pulmonary patients that are being treated with corticosteroids that have been measured with the Beck's Depression Inventory have had an increase in their mean scores. We also know with digoxin that you also have an increased score with the Beck's Depression Inventory. So, this is a tool that can be used. And the case with Accutane is that we do not get a confirmation of the signal.

Now, in the briefing document, you have a number of observational reports that are presented in the literature from a number of individuals that have been treated with high vitamin A doses or other retinoids and are trying to draw an association. What we could not do is establish a linkage between the retinol treated patients or the other retinoid treated patients based on their biological plausibility.

What you need to be able to do within a plausibility is not only to show that there are systems

available, but you have to show that there's functionality of the systems. So, one of the things that we wanted to look at carefully was to evaluate what was the functionality of the retinoid systems within the brain and also what was the evidence that was presented from these patients that had high doses of vitamin A. When you look at these anecdotal reports, then you see that these patients have been taking high doses for extremely long periods of time and are extensively elevated.

What we have then is that when we look at these types of information, we know that to be able to detect receptors using messenger RNA, which is the very beginning part of the signaling system, you can find specific dopamine enriched brain regions that do have retinoid receptors within adult animals.

However, we also know that these are not necessarily functional because the localization of these proteins differ from the localization by messenger RNA. You can have different detection methods to determine whether a receptor is present in the brain or not. Just having a message doesn't mean that the protein is there, and if the protein is there, you don't necessarily have the functionality of that receptor. If you had functional receptors, you would have different types of behaviors. For example, with the dopamine enriched areas, you would

expect some of the symptomatologies to be tremors or Parkinson's-like syndrome.

We also know that there are a number of different receptors that do have retinoid response elements. That means these are elements that can be regulated by retinoids. Dopamine receptor genes are one of the receptors that are pointed out.

Dr. Adams has mentioned that in the embryonic brain that there are a number of receptors that are responsible for hind brain. These are, for example, the Hox genes or the homeobox genes that are responsible for normal development. Well, the dopamine receptors that have been detected with active receptors are from cells that were embryonic or they were cells that were only in culture which have embryonic-like features. It's most likely that perhaps the dopamine receptors only respond to the retinoid when they're in the embryonic stage.

We also know that there's information that isotretinoin can be found in the brain after injections into animals. That's not surprising. It's a lipid soluble molecule, and many different types of lipid soluble molecules can bypass the blood-brain barrier. It doesn't imply that there's a functionality of that molecule in the brain.

So, although some of the component factors are

in place, retinoids have not been shown to activate genes to induce behavioral or psychiatric changes.

One of the other pieces of evidence that you can add to that is in mice lacking retinoid receptors, there's no major behavioral changes in these animals. They needed to do special studies in order to determine that in these animals the only effect they were able to observe was long-term memory changes. These were identified as long-term potentiation or long-term depressive changes, and these might have been involved during the development of the embryos when these receptors were absent during the embryonic development of the brain.

There's also a lack of evidence demonstrating the functionality of the retinoid signaling pathways in the mature central nervous system. There's no evidence in the literature of any of these signaling pathways being present. This was pointed out by Dr. Adams earlier yesterday in her discussion.

All of the available evidence then does not confirm a system. The biological plausibility of the signaling pathways with the retinoids has not been established. However, the background disease rate in the population warrants attention to signs and symptoms of the psychosocial disturbances by dermatologists.

At this point then, I'll turn this over to Dr.

Russell Ellison.

DR. ELLISON: I will try to be brief to keep on schedule. Thank you for this opportunity to wrap this up.

Just to review, the evidence that you've seen that we've generated to try to put these issues into perspective we do not believe supports a causal association of psychiatric illness with Accutane. The signal generated by the spontaneous reports that we discussed could not be confirmed. Indeed, specific information related to possible risk of events, even in an associated context beyond the known risk factors for disease, is lacking.

What we have observed is that patients with severe acne or acne in general come from a cohort which, depending on age, gender, and prior history, may be at high risk for concomitant illness.

So, when we're evaluating risk management issues around psychiatric events, where we have a degree of uncertainty around the causal association and we have little information about risk factors, we have to ask what information do we want to convey with what desired actions to be taken by whom and in what circumstances. We believe that to focus prescribers and patients only on the Accutane issues, particularly with respect to the uncertain causality at present, may lead them to miss the very high level and the likelihood that people could have psychiatric

disease irrespective of their acne treatment.

So, we see risk management in the context of psychiatric disease as a concomitant illness where, for example, with continuing medical education, you would alert the prescriber to this phenomenon with the possibility that he can use the treatment venue as an opportunity for identifying possible problems, that is to say, to enhance the overall medical impact of his practicing in this group of patients. But this would be applicable to all high risk patients and Accutane information would certainly be included so there can be a degree of vigilance.

For example, to ask the same questions about labeling. We think there's an opportunity with the professional labeling to certainly include the new Accutane data, to talk about the symptoms so that we're more informative, to talk about discontinuation if we can decide, indeed, what to do, and also to use this opportunity again to alert professionals to the comorbidity in all high risk patients.

For patients, we think there's an opportunity to certainly communicate the Accutane information that we know, to have them be alert to symptoms which can be described in laymen's language, to alert them to inform their physician of previous history, to be alert to the possibility of psychiatric illness, irrespective of

Accutane treatment as well. Not to do this would be to miss an opportunity to prevent disease and to manage it.

I haven't dealt with all of the options put forward in the questions, but I think these are fairly important ones. With respect to informed consent, this is an interesting issue because of the issues of the relative strength of a causal association compared to the other serious adverse events in the label which do not appear in the informed consent. I think more importantly is what would we be informing patients about, which would be relevant for them to be giving their consent to treatment without a strong statement of cause or estimates of risk.

Now, let's apply the same parameters to assessment before and during treatment. This would be monitoring in the questions that you have. Simple questionnaires, which can, in fact, be implemented in the waiting room, are available to identify the possibility of psychiatric illness, but simple screening tools cannot confirm or rule out this illness in the hands of a non-psychiatrist. So, for all high risk patients, this could become part of the dermatological assessment as a signal to refer the patient for psychiatric help irrespective of the treatment you're going to give them, but also you would include vigilance about Accutane itself in this regard.

The concern that we would have about this,

which would need to be addressed, would be the potential risk of conflict with the time needed for pregnancy prevention in women. We had a discussion yesterday about the time taken to provide the education, in the physician patient context, for a clear, known risk, with a very, very important job to do to prevent pregnancy. And adding more burden to the physician in this regard may, indeed, dilute this particular issue. This is a very hard call to make, but hopefully if one was going to do something, the waiting room questionnaire and the review for high risk patients, people coming from a cohort with a high background of disease may be helpful.

Now, finally formal studies. Before I go on to the details, which I'll keep short -- we can provide more information in the question period. I think it's first important to ask what will we do with the answer because then asks the question of what kind of answer do we need and what strength of an answer do we need, which then leads to the issue of what questions do we need to ask and how do we need to ask them.

With this respective problem, there are the following interesting difficulties. We have a unique drug, unique in the sense that for many patients nothing else will work. This has a lot of implications for the question we're going to ask and how we're going to ask it. We have

a relapsing, remitting illness. Even major depressive disorder is relapsing and remitting. We have soft endpoints to evaluate which are very susceptible to observer bias and placebo effect in patients, and as we've noted, we have a very high background prevalence rate with a low de novo incidence rate. So, this leads to problems.

We believe that it's probably almost impossible to definitively rule out or to confirm the signal with further studies. We think it's going to be very, very difficult to define, characterize or quantify the risk. We think it may be possible, to some extent, to decrease uncertainty, but again I'm not entirely sure what we would do with that answer. So, let me go through this.

First of all, from the prospective clinical trial question, I'll be brief. Obviously, with a unique drug, we have a problem with randomizing to a control group where only Accutane may be effective in someone who is facing lifelong facial disfigurement.

The hypotheses and sample size also become problematic for several reasons. First of all, with a low de novo incidence rate of about 1 percent in a 6-month period, we're looking at very large numbers. We have actually looked at an open design around this as an example of the difficulties, which we can speak to in the question period.

Finally, blinding of patients who are taking Accutane when 93 percent of them get Accutane side effects, many of which are easily identifiable as mucocutaneous effects, makes a blinded study almost impossible for inter-observer and patient bias.

With respect to open cohort studies, these would seem, on immediate inspection, to be more feasible and perhaps more interesting. The first problem is we will not find a matching cohort with respect to severity of disease because of the uniqueness of the drug, or at least it will be extremely difficult. The severity of acne, as we've heard from dermatologists, clearly relates to having depressive symptoms or disturbances of mood. Management of that disease can change those depressive symptoms or mood.

So, it really is going to depend on the specificity of the question you would ask and again the confidence you would need in the answer. Certainly these are going to have to be prospective. I think that is what was intended by the question.

I think in terms of time and feasibility and ability to further clarify these issues, perhaps you would imagine that retrospective epidemiological cohort studies would provide our best bet, and they may well do so. The question is going to be to find a good database, an available database that has the right size, specific

coding, and population definitions, and the methodology to manage the analysis of that database. The studies we did, even the power was probably only good enough to look at a risk that was two- or threefold the current prevalence. So, I think we would want to know a number that was much lower than that. So, I think the challenge there is going to be to define databases where we can indeed do this.

With respect to the last point, which is in vitro and in vivo preclinical studies, I think the issue here is to be careful that we are looking at specific models for specific psychiatric illnesses versus looking at general toxic reactions in the brain which have been observed with many drugs at very high doses that cross the blood-brain barrier because the sort of toxic reaction is not connected to the plausibility of causing major depressive illness or suicide. I think there are perhaps some models available. We have to be very careful with the dose so that we have extrapolatability and very careful about the extrapolatability of the model.

So, I think that sort of summarizes where we would go with studying this issue. It is fraught with problems. For the major answer, we believe it's essentially impossible.

Finally, our conclusions are again that the evidence does not support a causal association between

Accutane and psychiatric illness. The signal that was generated by the spontaneous report reviews which implied causation has not been confirmed by further evidence. Additional studies might somewhat clarify but certainly not definitively resolve these issues.

Now, much has been learned about psychiatric disease in acne patients and we believe there's an opportunity to enhance the overall medical impact of the management of all acne patients in a dermatological practice.

Thank you for your attention.

DR. BERGFELD: Thank you very much.

Our agenda shows us that we're going to break now for 15 minutes, after which the FDA will present with their multiple presenters, followed by the discussion of the committee. So, at this time I would like to call a 15-minute break and we will reassemble here at 10:35.

(Recess.)

DR. BERGFELD: Would you please take your seats?

I'm going to be changing the agenda slightly. We will have the FDA presentations, followed by the open public hearing. We will then adjourn for lunch at 12:15. We only have a half hour lunch today. So, it's 12:15 lunch. 12:55 we will reassemble, at which time we will

have committee discussion, answer of the questions posed to us by the FDA and a vote. Then at 1:55 we will move on to Accutane New Formulation. Again, we're changing the format, moving the public hearing up after the FDA presentations.

So, at this moment we will go forward with the FDA presentation. It's my understanding that Dr. Alan Byrne will speak to us on isotretinoin and depression.

DR. BYRNE: Thank you, Madam Chairman. Good morning.

I'm going to talk today about isotretinoin and depression. This basically is the clinical experience I've had in relation to my exposure to this drug. I'll give a little bit of a background now, if I could see the next slide, please.

I was working in the University of Alberta in the Psychiatry Department in 1993 and over a period of about 3 months, I was exposed to three cases of depression in young individuals. One of the most important factors I felt in relation to these individuals was they had all recently received isotretinoin therapy for acne, and their depression presentation was atypical.

I didn't know a whole lot about isotretinoin at that time, and I was alerted to the fact that it was a vitamin A derivative. This sparked a thought in my mind in

relation to a lecture I had in university in pharmacology where we were told about Arctic explorers in the early 1900s having developed psychosis following eating polar bear liver, which apparently has very, very high levels of vitamin A in it. So, it sparked my interest and I decided I would do a little bit of background work.

In relation to the cases, these there three young individuals. There was no previous history of depression, no family history of depressive illness. In all cases, there had been an abrupt deterioration in mood. The individuals had associated irritability which was very pronounced. They were very aggressive, particularly with family members, and this was out of character and new. As I mentioned, all three had recently used isotretinoin for acne.

I'll describe the individual case reports that I described initially first.

The first individual was a 28-year-old lady. She complained of low mood and agitation for approximately 8 months. She described marked irritability with family members to the extent that this had actually caused a deterioration in her relationship and the breakup of her marriage, but the irritability had predated the marital disharmony. She described poor sleep, poor appetite, and anhedonia, or a total absence of joy in her life. She had

had a 4-month period of treatment with Accutane during the year, and the depressive symptomatology had commenced during that period of time.

The second case was an 18-year-old male who had presented with having had an abrupt onset of depression whilst receiving isotretinoin therapy. He was aggressive with family members again, and he had had violent thoughts and violent outbursts. He had suicidal preoccupation, and by the time he actually was referred to me, he had actually taken an overdose of tablets, from which he had recovered. There were no obvious precipitants in this young man's history. He had no previous history of any psychopathology. There was no family history of any psychiatric illness. And he had biological symptoms consistent with a depressive illness which were altered sleep and appetite which had been present for some weeks at the time I saw him.

The third case was one of the most impressive in terms of my deciding that there might be an association with isotretinoin, and I'll expand on this now. It was a 21-year-old girl who had severe, resistant depression. She had had months of agitation and aggression which was evident at home. She described poor appetite, poor sleep and weight loss, and her response to antidepressants from a general practice perspective had been very poor, so she was

referred to the university for assessment.

She actually had to be admitted to hospital, so severe were her depressive symptoms, and whilst in hospital, she was taking isotretinoin of her own that she had brought into hospital, which we were unaware of, and her symptoms remained unresponsive until we stopped the isotretinoin, took away her supply, continued her antidepressants, and the depression responded. Again, this lady was treated with antidepressants and she remained well on antidepressants when she got off the isotretinoin.

So, in relation to my queries and concerns in relation to isotretinoin, I discovered that it has a very extensive list of ADRs. It's a fat soluble vitamin A derivative. The mode of action is unknown. And in making inquiries in the university, the dermatologists on staff were completely unaware of any problems in relation to mood or psychological disturbance in relation to this drug.

So, we did a literature review. At that time in 1993, there were almost no articles of note in English. There were several articles in the French literature which questioned the possibility of psychological disturbances in relation to the use of isotretinoin. One of the articles in English that was pertinent I felt was one by Scheinman. He indicated that he seen depression in 1 percent of users of isotretinoin. Out of 700 cases, 7 people had become

depressed and had to be withdrawn.

There was further a letter by Gatti and Serri who described a case of suicide in an individual who had recently received isotretinoin.

And Bravard in France described a case of suicide in a young man receiving isotretinoin, and he urged caution in relation to the use of this agent. That article was in French and had to be translated for me.

So, further to the discovery that there was actually a precedent in relation to psychological disturbance in relation to the use of this agent, I published a letter in the Canadian Journal of Psychiatry in 1993 alerting my psychiatric colleagues to the fact that there was a possibility that depressive symptomatology might emerge in people receiving Accutane therapy, isotretinoin.

I actually left Canada in 1994 voluntarily.

(Laughter.)

DR. BYRNE: And I returned to work in Ireland where I actually was exposed to further cases of individuals who had depressive symptomatology following use of isotretinoin, and I published a series of cases in the Irish Journal of Psychological Medicine in 1996 along similar lines to the cases I had seen in Canada.

Since 1995, by virtue of the publications I

have had in this area, I've had an increasing number of contacts from patients with depression who have associated their depressive symptomatology with the use of this agent. Individuals generally tend to describe depressive mood, agitation, not infrequently suicidal ideation, and they have also described behavioral change which can often be very bizarre and very unpredictable. One of the major factors that was a concern to me is that these individuals tend to describe a chronic apathy and dysthymia that extends far beyond the use of the drug and appears to continue over time, often without treatment because it hasn't been recognized or diagnosed by people they go to see.

One major concern I had was that obviously if people developed depressive symptomatology, the reality is they're not going to mention this or go with this to a dermatologist per se, and therefore it was important, I felt, that people in the psychiatric arena would have knowledge of the fact that this agent might be associated with depressive symptomatology.

As I've said, in relation to my other clinical experience with isotretinoin over the last 5 or 6 years, I've seen more than 20 cases in total. Most of these are young individuals. Most would have had recent use of isotretinoin, but there can be quite a considerable

variation, a little bit like postpartum depressive illness which can come on late after the birth of a child and carry on then for some time. I've seen individuals who have described mood change some months after discontinuing isotretinoin and then this mood change has been pervasive and persistent over time.

The ratio in the individuals I've seen is approximately, female to male, 2 as to 1 in terms of depressive symptomatology.

One observation I have made, which may or may not be of tremendous significance is that this seems to come on in thin, physically fit individuals. The only rationale or the only theory I've had in relation to that is because isotretinoin is lipid soluble and the relative lipid content of the body will be lower vis-a-vis body to brain in fit individuals, as opposed to more obese individuals, and that more of the drug might end up in the brain fat tissue as opposed to in the body fat tissue in the thin or fit individuals.

The other observation I've made is that the symptoms can be extremely protracted, and I still have a number of individuals who I am treating with antidepressant medication for protracted periods at the moment.

Therefore, in relation to isotretinoin, my clinical observations have been that this agent can

influence mood in certain individuals.

My feeling is that the effects on mood may be very persistent, and obviously anything that can precipitate a depressive illness may be life-threatening because there is a significant risk of suicide with depressive illness.

My observation as well is that the effects seem to be most pronounced in thin, athletic individuals who have a low body fat content, and I feel that this probably relates to lipid solubility.

Thank you.

DR. BERGFELD: Thank you very much.

We're going to proceed then to the second presenter which is Dr. Erick Turner, drug-induced depression.

DR. TURNER: Well, thank you.

The title of my talk is Drug-induced Depression. The purpose of the talk is to give basically an overview of depression and drug-induced depression primarily for the benefit of the non-psychiatrists, of whom I am certain there are many here today.

So, this will be the first of several FDA talks. The talk after mine will be a case review by Dr. Marilyn Pitts, followed by postmarket experience by Diane Wysowski; biological plausibility and options for risk

management by Dr. Kathryn O'Connell.

Now, before talking about drug-induced depression, I'm going to back up and talk about what we probably know a lot more about, and that's major depressive disorder. Major depressive disorder is what psychiatrists usually but not always mean when they talk about depression or what lay people probably usually mean when they talk about "clinical depression." There are other types of mood disorders certainly and even other types of depressive disorders, but this probably the one recognized as the most frequent and most serious. So, I will lead in with a discussion of that.

I have up there DSM-IV diagnosis, and let me just quickly explain what that refers to. DSM is the Diagnostic and Statistical Manual, Fourth Edition, and this is a manual which the field agrees upon contains the criteria by which we diagnose various types of mental disorders and that facilitates agreement between clinicians so that we all know that we're literally on the same page, as well as various researchers so that again we know we're all studying the same thing. Otherwise, before the DSM series came out, the meaning of the word "depression" was very idiosyncratic.

So, the DSM-IV criteria require a duration of at least 2 weeks. The symptoms have to be present most of

the day nearly every day, so it has to be a pervasive mood disturbance. And they must be clinically significant. This is more than just a bad hair day, if you will. It has to cause significant distress or impairment in one's social or occupational functioning, so perhaps affecting one's marital or family relationships or even interfering with one's ability to function effectively at work.

Now, this is a somewhat busy slide, but I'll walk you through it slowly. First of all, the title "Symptoms of Depression," this is not all depression. Depression again means different things to different people, but here I'm referring to major depressive disorder. This is to be contrasted with drug-induced depression which I'll move into later.

I have nine symptoms listed here and I have them broadly categorized into two categories. You won't find this categorization in DSM-IV, but it may be useful as a way of understanding them. First of all, the psychological symptoms and the neurovegetative symptoms.

Among the psychological symptoms, we have depressed mood. Loss of interest or pleasure, and by that, a person may experience that as a decreased motivation, a loss of interest in one's work, they don't enjoy their job as much as they used to, for instance. Feelings of worthlessness or guilt, and also suicidality or thoughts of

death. Again, these symptoms are not all required but just five of the total number of nine here on the list.

Let me come back to the first two symptoms I have listed there, depressed mood and loss of interest or pleasure in things. The reason I have those underlined is because at least one of those symptoms is, in fact, required to make a DSM-IV diagnosis of major depressive disorder. So, in other words, if they have several neurovegetative symptoms and even theoretically suicidality, it's possible not to qualify for an official, if you will, DSM-IV diagnosis.

I also want to highlight that I said "or," depressed mood "or" loss of interest or pleasure. Some people may not express depressed mood. They may not even experience depressed mood when specifically asked about that, but they may have anhedonia, again this loss of interest or pleasure. So, that's perhaps more likely to be missed than someone who spontaneously complains of depression.

The neurovegetative symptoms are what we might think of as the more biological symptoms. The depression is evidence of this being a true biological process going on in the body with a life of its own, so to speak, again more than just a bad mood. They include changes in appetite and weight, and that can be in either direction.

It can be decreased appetite or increased appetite, likewise with weight. Sleep. You can have insomnia or hypersomnia. The person might be slowed down or agitated, and according to DSM-IV, the person should be visibly slowed down or agitated, not just subjectively so. Energy is often decreased. The person feels tired. They might think that they have anemia, for instance. Concentration might be decreased or they might have difficulty making decisions.

One other thing is to highlight again the depressed mood or the anhedonia. Not only is one of those two symptoms required to make the diagnosis of major depressive disorder, but to make a formal DSM-IV diagnosis of substance-induced depression, that is about all that's truly required to make the diagnosis. So, it seems that the threshold is higher with DSM-IV, at least with regard to the symptomatology, to make the diagnosis.

The neurovegetative symptoms are conspicuously missing, and perhaps the reason for that is one would have to have sat on the DSM-IV committee, but just to speculate, various medical conditions and medications might cause various neurovegetative symptoms. You can imagine drugs which cause a change in appetite or insomnia by themselves, and that might just confuse the picture. So, I think my speculation is that the committee didn't want to get tied

down saying that the neurovegetative symptoms were required to make a formal diagnosis of drug-induced depression.

The first two are, of course, symptoms, if you will, of both major depressive disorder and drug-induced depression.

The time course of depression -- again, I'm talking about major depressive disorder. The symptoms often develop over days to weeks, and the DSM-IV requires at least 2 weeks of symptoms.

If left untreated, the full syndrome can often last for 6 months or more. So, it may be almost as if a switch has been thrown and it may go for a longer time than seems to be warranted by the psychosocial situation. Indeed, the biology seems to have kicked in.

Residual symptoms can last months to years.

If treated -- and by this, I mean pharmacologic treatment -- a clinical response usually becomes evident in 2 to 4 weeks. So, this is the party line. Certainly not everyone responds to antidepressants, but 60 to 70 percent of people will respond to a given antidepressant.

Depression is a common disorder, and this point has been made previously by Dr. Nelson, I believe Dr. Jacobs as well. This is problematic, also as mentioned before, because it makes detection of drug-induced depression by spontaneous reporting especially difficult.

We're not talking about a very, very rare entity such as Stevens-Johnson syndrome or hepatic necrosis, but something on the other hand that has a lifetime prevalence of about 15 percent. The numbers will vary according to one's source and the time frame one is looking at. But anyhow, a fairly common, current prevalence of 3 to 6 percent among adolescents, and a 5 percent neighborhood consistent with overall prevalence.

I'd like to point out that these rates are gathered via epidemiological methods using random sampling of the population in which a sample is queried on all symptoms of depression using perhaps, going through formally the DSM-IV symptoms or using some other questionnaire that comprehensively covers various symptoms. If, on the other hand, one waited for spontaneous reports to emerge, undoubtedly the rates would be much lower waiting for patients to go and say, doctor, I believe I may be suffering from major depression.

Just a related point, I guess Dr. Nelson I believe mentioned that many of these spontaneous reports frequently don't have a formal diagnosis, and I guess that might be expected if psychiatrists aren't the ones making the diagnosis and they don't have the training to be familiar with the DSM-IV criteria.

So, depression is not only common, but it's

under-recognized. The symptoms are often not recognized as part of the depressive syndrome especially, for instance, the neurovegetative symptoms that I mentioned. Some people may not recognize concentration, decreased energy in the absence of depressed mood. And again, depressed mood is not strictly required for a diagnosis of major depressive disorder. You can have just have anhedonia.

Symptoms are often not obvious and cannot be proven with an x-ray or lab test which may lead to some increased reluctance on the part of the person to come forward and they might dismiss it thinking, well, maybe it's all just in my head. Maybe I'm just not trying hard enough, which is a point which comes below that symptoms often get dismissed, by both the person experiencing the depression, as well as perhaps family members or possibility even health care professionals. Symptoms might be dismissed as an appropriate reaction to stress, evidence that the person is not trying hard enough, or even a conscious attempt to achieve secondary gain.

Only about half the persons with major depressive disorder ever receive treatment. Dr. Jacobs had a somewhat lower number, about 40 percent. That's the "ever" category, and the current episode was down around 20 percent.

Adolescent depression may be especially under-

recognized. Again, I apologize for the redundancy, but these are points that keep coming up. Dr. Jacobs was making this point. Adolescents often will present atypically. They seem to be less likely than adults to display the neurovegetative symptoms and more likely than adults to show social withdrawal, irritability, or behavioral problems. And I believe Dr. Jacobs mentioned that adolescents might often conceal symptoms. So, all this adds to the under-recognition, under-reporting of depression and perhaps more so among adolescents.

Use of drugs and alcohol may be seen as the reason for behavioral changes. Drugs and alcohol can certainly be a confounding factor. On the other hand, drugs and alcohol might also represent a method of self-medicating one's depression or simply a co-existence or comorbidity of the two diagnoses. Perhaps they have no relation whatsoever. But in any case, if drugs and alcohol are present, they may be identified as the reason the person seems to be exhibiting these other symptoms, and there may not be a systematic probing into the other symptoms in consideration that the person might have serious depression.

The signs of depression often are seen as normal mood swings typical for the age group, and there may be a reluctance to label adolescents with a mental illness

diagnosis. This is the stigma issue that has been talked about quite a bit in psychiatry over recent years and applies to adults as well as adolescents. Depression and mental illness in general, for that matter.

Depression and suicide. Suicide is certainly the ultimate adverse outcome of depression. The Adverse Event Reporting System -- that's what AERS stands for, and that's what we've been talking so far today and we'll continue to talk about the spontaneous reports -- can generate signals, but the system should be considered inadequate for establishing or ruling out a link between Accutane and suicide. Again, it can generate signals and put us on the right path.

One reason that this may be the case -- there are several reasons, and I don't want to go into any detail. Although suicide is certainly a tragic outcome of depression, as we'll see on the next slide, which I'm not quite ready for unfortunately, is not nearly so rare as the sorts of disorders that are easily picked up by the adverse event reporting system, again the very rare things. Again, AERS is a voluntary system.

15 percent of mood disorders subsequently end in suicide, and 45 to 70 percent of suicides have a mood disorder. So, this is a mood disorder that's broader than major depression and would also include bipolar disorder as

well.

Outside of mood disorders, the other 30 to 55 percent of people completing suicides include diagnoses such as schizophrenia, alcohol dependence, other substance dependence and personality disorders.

A bit about the epidemiology. Again, I fear I'm being redundant, to some extent, with Dr. Jacobs' talk. The rate is about 30,000 per year. This seems to be a fairly consistent number, and it's the eighth leading cause of death. These numbers I got from the CDC website, the Centers for Disease Control.

For adolescents -- now, the absolute number will vary according to the age range one chooses. If I remember correctly, I chose a range of 11 to 20 for adolescents, which was the definition of adolescents according to a textbook I referred to. I believe others have used a range of 15 to 24, and you'll get higher numbers.

But in either case, it doesn't matter the absolute number here, but rather it's the relative number. It's the third leading cause of death among adolescents, and this is after accidents and homicide.

There's a gender effect. Women and girls have more attempts, but men and boys have more completed suicides. So, they attempt less often but succeed, if you

will, more frequently.

Moving a bit more to drug-induced psychiatric disorders, this gets to be a bit murkier for several reasons. Diagnosis is rarely clear-cut. The clinical features can vary with different drugs. I have different mechanisms. Perhaps I should have said different pharmacologic effects. It's possible some day in the year 2100 or so, when we truly understand depression, we will understand the mechanism for depression and understand all the various drugs and other causes, if you will, of depression all go through some final common pathway. So, we don't really truly understand the mechanism of depression. We do know some things that seem to be associated with depression.

But different drugs will have different pharmacologic effects, and so it can appear very differently and it's hard to come up with a set of criteria and something to tell clinicians what they should be looking for.

The clinical features can vary not only with different drugs but also with the same drug. One example of that is corticosteroids which can cause mood changes in either direction, depression or mania. They can cause anxiety symptoms or even psychosis. Overall I would have to say there's a lack of consensus. The evidence is