FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

8:35 a.m.

Monday, September 18, 2000

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2 Montgomery Village Avenue
Gaithersburg, Maryland

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

(8:35 a.m.)

DR. BERGFELD: Good morning. I'm Dr. Wilma Bergfeld, the acting chairperson for this Accutane advisory committee meeting, the two-day meeting. We'll meet today, September 18th, and the 19th. We have a two-day meeting that will comprise first today the Accutane pregnancy prevention program, which will involve the FDA presentation and Roche presentation. This afternoon we will have an open public hearing. We already have many scheduled presenters. If there is someone in the audience who has to present, will you please see Ms. Kimberly Topper.

(Audio failure.)

DR. BERGFELD: Again, welcome to the FDA's Accutane advisory committee.

As I was saying, this morning we will deal with Accutane's pregnancy prevention program, and I wanted to again mention the open public hearing time, which is scheduled for 1:45 p.m., and you need to be scheduled to present there. Tomorrow we will take up Accutane-associated psychiatric events and Accutane new formulations.

This is to be a very busy meeting. There will be many statements stated and lots of comment, and so I will control the meeting and limit the conversations if

it's appropriate.

At this time, however, I think we need to meet the diverse committee members. Some are voting and some are non-voting. I would like to begin here with you in the blue, if you don't mind introducing yourself, and we'll go around the table, including the table in front of me.

DR. MURPHY: Dr. Dianne Murphy, Associate Director for Pediatrics at CDER.

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

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

DR. WOODCOCK: I'm Janet Woodcock. I'm Director of the Center for Drug Evaluation and Research at the FDA, and I'll point out the FDA members are not panel members here.

DR. VEGA: I'm Amarilys Vega, medical officer from the Office of Postmarketing Drug Risk Assessment.

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

DR. ROSENBERG: Bill Rosenberg from the Division of Dermatology, University of Tennessee College of Medicine in Memphis.

DR. CRAGAN: Jan Cragan, Birth Defects and Pediatric Genetics Branch, CDC.

DR. GREENE: I'm Mike Greene. I'm Director of the Maternal/Fetal Medicine at Massachusetts General Hospital and Associate Professor at Harvard Medical School.

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

DR. MILLER: Fred Miller, Director of Dermatology, Geisinger Medical Center in Pennsylvania.

DR. KING: Lloyd King, Director of Dermatology at Vanderbilt University and the Nashville VA hospital, Nashville, Tennessee.

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

DR. MALONE: Richard Malone, child psychiatry, MCP Hanneman University in Philadelphia.

DR. BRANCH: Bob Branch, from the University of Pittsburgh, Director of the Center for Clinical Pharmacology.

DR. HOLMBOE: My name is Eric Holmboe. I'm a general internist and I'm from Yale University.

MR. LEVIN: Arthur Levin, Director of the Center for Medical Consumers, a consumer advocacy organization in New York City.

DR. GLORIA ANDERSON: Gloria Anderson, Callaway

Professor of Chemistry at Morris Brown College in Atlanta.

DR. ABEL: Elizabeth Abel, clinical professor of dermatology at Stanford and practicing dermatologist in Mountain View, California.

DR. JENNIFER ANDERSON: Jennifer Anderson, biostatistician, professor of biostatistics at Boston University, and also working at the Bedford VA in Massachusetts.

DR. TAN: Ming Tan from St. Jude Children's Research Hospital, and associate member of the Department of Biostatistics there.

DR. JONES: I'm afraid this doesn't go on, but I'm Ken Jones from the Department of Pediatrics at the University of California, San Diego.

DR. MILLS: I'm Jim Mills. I'm at the National Institute of Child Health and Human Development.

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

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

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

DR. RACZKOWSKI: Victor Raczkowski. I'm the Deputy Director in the Office of Drug Evaluation III at the

FDA.

DR. HONIG: Peter Honig from the Office of Postmarketing Drug Risk Assessment, Center for Drugs.

DR. BERGFELD: Well, thank you very much. You see that we have gathered together many, many experts from many diverse fields, including the FDA's expertise.

We're going to now proceed to the meeting statement, being presented by Kimberly Topper, the Executive Secretary for the meeting.

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 issue, 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 very much.

We are now going to proceed with the opening comments by Jonca Bull.

DR. BULL: Good morning. I first want to extend thanks to everyone here who has taken time from their busy schedules to attend this meeting. I particularly want to thank the advisory committee members for their commitment of time, intellect, and willingness to share these talents on behalf of the American public in addressing these important public health issues.

My task this morning is to delineate for the committee, our discussants, and the public the purpose of this meeting on Accutane.

The context of this advisory committee is unique in several respects. Accutane is a drug that has been marketed for over 18 years. Few drugs have engendered the level of involvement by the agency and a sponsor in ensuring safe use in both past advisory committees and internal meetings. Few drugs are as explicitly labeled as Accutane, and I would bring your attention to the size of those black box warnings that are currently part of the label for Accutane.

You might ask, why now? What is new? You would suppose that after 18 years we would have it all figured out, but the truth of the matter is that we don't, particularly in concerns as to the sufficiency of risk management.

Accutane is a highly effective drug in the treatment of cystic nodular acne. Accutane has a well-characterized risk profile as a teratogen, but also an evolving risk profile of uncertain risk for psychiatric adverse events.

For known risk of pregnancy and teratogenicity, are current programs adequate to reduce these risks to their minimum? What should be the goals to assess the sufficiency of management of these known risks?

Historically, regulatory efforts have repeatedly over the years been directed to improve the professional labeling and packaging of the product in order to fully inform patients and physicians of the risk associated with its use, particularly the teratogenic risk during pregnancy. Additionally, through a contract with Hoffmann-LaRoche, the Slone Epidemiology Unit at Boston University has tracked Accutane users who elect to participate in this program.

As will be shown today in data from several surveillance sources, the FDA, Hoffmann-LaRoche, and Slone,

there is a persistent and disturbing body of data of pregnancy exposures. We also know that these databases reflect a significant level of under-reporting of these events.

The fundamental question is, from a risk management standpoint, can we in our mission to ensure the safe and effective use of drug products, given societal and regulatory realities, develop a framework that further reduces the known risk of teratogenicity attendant to the use of this drug product?

Indeed, some of these issues may not be answerable. There may well be areas, for example, limiting distribution or mandatory registries, that you, the committee, may deem not appropriate for government to be involved in.

From a risk management standpoint, looking toward our day two, for 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? 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?

As ordinary citizens in our daily lives, we

must regularly assess risk in making decisions. We know that risks are ubiquitous in our modern society. We know that all drugs have benefits and risk. We have a responsibility as a public health protection agency, along with you, our expert panel, the advocates with us today, the manufacturer, and health care providers to the very best of our collective abilities to ensure a risk management framework for therapeutic decisions that maximizes the beneficial and safe use of Accutane.

We are here today because opportunities exist for improvement. Clearly it is in everyone's best interest to get all these issues out on the table, to try to assess risk and examine a variety of options for risk management. We welcome this opportunity for discussion as we learn from your experience, knowledge, and perspectives on the issues. We have asked for and need your help and advice.

Now for an overview of our day one. In presentations this morning, our first two FDA discussants will address the agency's evolving risk management framework. Dr. Victor Raczkowski will present to you on risk management options for marketed drugs, followed by Dr. Peter Honig, who will provide a post-marketing perspective. These talks will be followed by the FDA presentation on the pregnancy prevention program and on Accutane and its clinical background and regulatory history. This will be

followed by a guest presentation by Dr. Edward Lammer on pregnancy exposures and teratogenicity. Following the presentations by Roche in the open public hearing, Dr. Vega will discuss potential design elements for risk management and pregnancy prevention.

In closing, I must acknowledge the hard work and the commitment of all of our FDA scientists who have applied themselves with dedication to the complex and difficult task involved in preparing for this meeting. Thank you.

DR. BERGFELD: Thank you very much, Dr. Bull. I must say that the materials presented to the committee members were outstanding and we appreciate them.

We're going to move on, then, to the risk management options for marketed drugs presentation by Victor Raczkowski.

DR. RACZKOWSKI: Good morning.

Once the safety issue has been identified, the issue arises as to what should be done subsequently, what sort of risk management interventions should be taken. In my talk today I will briefly summarize some of the options that are available to FDA and to sponsors in terms of risk management.

The first three options, labeling, communications and educational programs, and advertising,

can basically be grouped into risk communication, and altering risk communication in order to decrease adverse events.

The next two items, packaging and restricted distribution, are more formalized methods by which the distribution of the drug is limited, either to physicians or other health care practitioners, those who are dispensing the drug, or to patients.

I will also touch upon the importance of monitoring the effects of the risk management program, and we'll talk about informed consent.

Then ultimately once a drug is on the market and has been shown to have an unacceptable risk-benefit profile then the product can be withdrawn.

Labeling is one of the main risk management tools and risk communication tools that FDA has used over the years, and labeling refers not only to the labels which are the labels that are placed on the immediate container and package, but also refers to the package insert, which contains both professional labeling, and in some instances patient package inserts and other information for patients. I will also talk about a new regulatory mechanism that we have now which are called medication guides.

Patient package inserts are essentially extensions of the professional labeling. They can be

distributed to patients when the drug is dispensed, and they provide important language about a drug in lay terms so that the patient and other consumers are able to understand the information and perhaps take steps to prevent serious harm.

In contrast, there is a new mechanism that FDA now has which are called medication guides, which became effective by regulations that were published in the end of 1998 and which became effective in June of 1999. In contrast to patient package inserts, what medication guides are, they are also leaflets for patients, but they are required to be distributed to patients whenever a prescription is filled or refilled. Moreover, medication guides may be used with unit-of-use packaging to enforce their distribution.

So again, just to summarize some of the main differences between patient package inserts and medication guides is that they must be distributed whenever a prescription is filled or refilled, and they also have a standard content and format which is approved by the FDA.

In terms of the professional labeling, there are many areas of professional labeling which identify serious risks, but the two most important are the contraindications section, which refers to risks that are so serious that they clearly outweigh any potential benefit

of using the drug. Another category are boxed warnings. Boxed warnings refer to serious risks, and particularly those reactions that are serious in proportion to the potential benefit that might be achieved from the drug. Boxed warnings are oftentimes imposed when a benefit risk should be considered before a drug is prescribed.

Boxed warnings also refer to serious adverse reactions that can be prevented or decreased in frequency and/or severity. For example, Accutane currently has a boxed warning for its use in pregnancy. Boxed warnings describe contraindicated situations, and they also provide important risk benefit information about a drug.

In addition to the labeling, both professional labeling, patient package inserts, and medication guides, there are other sorts of risk communication mechanisms that can be used. These fall under categories of communications to healthcare practitioners and consumers. Dear Healthcare Practitioner letters are letters that are provided by and written by the sponsor, and that are mailed to different healthcare practitioners, describing significant risks associated with the drug. In addition, companies and the FDA can release press releases to describe things. And FDA also has another mechanism to provide talk papers, which are posted on an FDA web site whenever risks have been identified.

In addition, there are health advisories that can communicate serious health risks, and there are educational programs that are sponsored by the drug manufacturer which are directed to health care practitioners to ensure the drug's optimal use and implementation of necessary precautions.

In addition to those educational programs, educational programs can be directed to the public and to the patients through toll-free numbers, Internet sites, newsletters, and collaborative efforts with patient advocacy groups.

Finally, sales force outreach is another risk communication mechanism that sponsors can use in order to alert health care practitioners of significant adverse events associated with the drug.

Advertising is the third main category of risk communication, and there are several ways that advertising can be used or restricted in order to serve a risk management function. One is to voluntarily restrict advertising to a specific general type. The second is to voluntarily restrict direct-to-consumer advertising.

In general, advertising must present a brief and accurate and balanced representation of adverse reactions, contraindications, and effectiveness. Reminder ads, which are simply advertisements that draw attention

only to the name of the drug, are not permitted for drugs with a boxed warning.

The third major category is packaging and restricted distribution. Packaging can be manufactured such that whenever the product is distributed it is automatically distributed either with a patient package insert or a medication guide, and that is called unit-of-dose packaging.

In addition, under certain circumstances restricted distribution can be employed. What restricted distribution is is a mechanism to ensure safer use and availability of a specific drug over existing treatments to treat serious or life-threatening conditions.

Restriction may be either voluntary, or it may be required. There are a number of drugs that are on the market that do have restricted distribution either to physicians or to dispensers.

Finally, informed consent is a mechanism that provides the opportunity for the patient to consider whether or not to take the drug. Accutane has a consent form at the end of its package insert. However, this informed consent form is a voluntary one, which primarily deals with the risk of teratogenicity of the drug.

Information in informed consent should be in language understandable to the patient, and it cannot

contain language to waive the patient's legal rights, and cannot contain language to release others from liability or negligence.

Once risk management interventions have been undertaken, it's important also to evaluate whether they are having the desired impact because implementation of a risk management intervention or risk management plan may not lead to the desired outcome. In other words, increased knowledge may not translate into desired changes in behavior. So, the success of risk management plans should be assessed. Once they are assessed, the results can then be used to tailor the risk management strategy.

As I've mentioned, withdrawal is the ultimate risk management tool, which can be either voluntary withdrawal by the sponsor or withdrawal of approval of an imminent hazard.

Finally, risk assessment is important because there may be need for additional studies to evaluate risk. For example, the etiology of a risk or other risk factors or incidence of a risk. However, a risk management plan can often be implemented concurrently with such studies that are intended to assess risk. In other words, it is not necessary oftentimes, if a risk has been identified, to formally assess the risk first and etiology prior to instituting a risk management plan.

So, in conclusion, there are many options that are available to help manage risk for Accutane, and I've tried to provide the whole broad spectrum, all the way from labeling changes and other risk communication techniques, through restricted distribution and withdrawal. Interventions will be considered.

So, several points for consideration that we would like the panel to consider are to consider which risk management pools should be used for Accutane. Consider next steps if the goals of a risk management program for Accutane are not being realized. And then consider when additional risk management tools should be implemented. In other words, what defines success and failure of a risk management plan, and when would you consider going to the next step, or using an additional risk intervention tool.

Thank you.

DR. BERGFELD: Thank you very much. You have set the stage for some of the discussion later on this morning. We'll now proceed to the next presenter, a postmarketing perspective, Dr. Peter Honig.

DR. HONIG: Good morning. My name is Peter Honig. I'm from the Office of Postmarketing Drug Risk Assessment.

As you've heard from Dr. Raczkowski, there are a variety of risk management and risk communication options

available to FDA and the pharmaceutical manufacturer. Traditionally we have relied on product labeling and/or re-labeling and relatively passive strategies such as Dear Doctor letters and educational efforts to attempt to optimize the benefit-risk of marketed drugs.

I was asked in 15 minutes to give a brief postmarketing perspective on the relative effectiveness of these strategies. I thought this might best be done in the context of some recent FDA experiences and examples.

Before you is a partial list of drugs that have been removed from the market in the last three years or so. They share the property of having known safety problems, either identified at the time of approval or in the post-marketing phase, that were largely preventable if the drugs had been used appropriately. I will briefly discuss each of them and attempt to frame the risk management lessons each has provided to the agency.

Seldane, terfenadine, the first non-sedating antihistamine approved in the United States in 1985. Its secondary pharmacologic effect on cardiac repolarization was not appreciated at the time of approval. However, reports of QT interval prolongation and torsade de pointes were received by the agency shortly after approval. Eventually its mechanism of the cardiac repolarization abnormalities were appreciated largely through the

pertubation of its metabolism, in the case of use with contraindicated drugs which impaired its metabolism or in the presence of hepatic failure.

Nevertheless, serial labeling changes, Dear Doctor letters, and educational campaigns were attempted to manage the risk. This was one of the first examples in which the FDA attempted to quantify the effect of its risk management and risk communication efforts, and in looking at a managed care database, it was apparent that there was residual, recalcitrant co-prescribing going on, despite the re-labeling changes in the Dear Doctor letters. Eventually, as we know, this drug was voluntarily withdrawn from the market.

I think the lesson we've taken away from that is that postmarketing labeling changes in a widely prescribed product were relatively ineffective.

Mibefradil, trade name Posicor. This drug did benefit from the legacy of terfenadine in that its potential for drug-drug interactions was clearly identified prior to approval and the drug was painstakingly labeled for its potential to interact with other drugs. It was a calcium channel blocker approved for hypertension in 1997.

Shortly after approval, reports of serious injury due to drug-drug interactions were received by the agency, and again, serial labeling changes, Dear Doctor

letters, an FDA warning, as well as educational efforts were attempted to manage the risk. Reports continued to be received by FDA, and eventually this drug was voluntarily withdrawn, approximately one year after its approval.

Again, the lesson we learned from this was that detailed labeling, even at the time of launch, with subsequent labeling changes were ineffective at completely managing the risk of this product.

Duract, bromphenac. This was a non-steroidal anti-inflammatory drug approved in July '97 for the short-term management of acute pain, labeled to be used for 10 days or less. And this was largely labeled because of the higher incidence of increased liver enzymes that were seen in clinical trials that appeared to be related to cumulative exposure.

Shortly after approval, reports of severe hepatitis, as well as acute liver failure were received by the agency. Labeling changes and Dear Doctor letters were attempted in early 1998. However, there was evidence that the drug was being used in a chronic manner for more than 10 days, as well as additional reports of hepatic injury being received by the agency, which led to its voluntary withdrawal from the market in June 1998.

Again, the lesson that we have here is that

initial as well as postmarketing risk management, risk communication efforts were relatively ineffective at managing the risk from this relatively effective drug.

Then finally I offer Propulsid as an example, a drug whose secondary pharmacologic properties and its effect on cardiac repolarization was not appreciated at the time of approval in 1993 for nocturnal heartburn.

Shortly after approval, reports of QT prolongation, torsade de pointes, and death were reported and received by the agency. Eventually the mechanism of injury and the risk factors were, indeed, well described and situated in the product label.

Serial labeling changes over the life cycle of this drug, Dear Doctor letters, as well as intensive educational campaigns were relatively ineffective at managing the risk. Reports continued to be received, and most recently a study was done in two managed care databases and a Medicaid database showing us that even after the most recent labeling change and Dear Doctor letters, 22 to 53 percent of cisapride use was in contra-indicated conditions, which was relatively unchanged from after the risk management strategy.

The lesson here was, again, that serial postmarketing labeling changes, as well as passive information dissemination strategies, had little effect on

the risk of this drug.

So, what are the lessons learned we have from these examples? I think it's clear that labeling changes and Dear Doctor letters are relatively ineffective ways of communicating risk if your intention is changing behavior.

We also, I think, with the cisapride example, with seven years of serial labeling changes and Dear Doctor letters, introduced the concept of labeling fatigue and the law of diminishing returns coming into play here, that if the inappropriate or the unsafe prescribing behavior is not modified after the first or second labeling change, one really can't expect to have dramatic improvements with the fifth or sixth labeling change.

As Dr. Raczowski said, labeling and labeling changes do not necessarily equate into knowledge, either on the part of the consumer or the prescriber, and even if that knowledge is disseminated to the prescriber it does not necessarily translate into behavior.

So, clearly if we're going to address the issue of knowledge not necessarily translating into behavior, is there a fundamental question here, that knowledge overload is the problem? I think I would submit to the committee that health care providers are probably not lacking for the information or access into the information. It's putting it into practice that's the problem.

And maybe we can look to some of the other experiences, perhaps from the Agency for Healthcare Research and Quality which are TRIP and PORT initiatives. TRIP is the Translating Research Into Practice initiative, and PORT is the Pharmaceutical Outcomes Research Team initiative.

I would just cite two examples there, in the use of beta-blockers post-MI, post myocardial infarction. BHAD is now a quarter of a century old, and still eligible patients after myocardial infarction are not being beta-blocked in a dramatic manner. Still only 40 percent of those eligible patients are getting beta-blocked, which is clearly known lifesaving therapy. Most recently it's been elucidated that beta-blockers, when used appropriately in congestive heart failure, are also lifesaving therapies. It's quite evident that this knowledge is not being translated into prescribing practice by and large.

In closing, I'd like just to cite an article that appeared in JAMA last year, entitled "Why Don't Physicians Follow Clinical Practice Guidelines?" It addresses some of the impediments to translating knowledge into behavior, and it clearly has application to the risk management and risk communication questions that are being addressed here.

What they looked at were several thousand

studies and their objective was to identify the barriers to adherence to clinical practice guidelines. Six major barriers were identified. As I discuss each of them, think about how these barriers would apply to each of the drugs I've cited as examples, as well as to the safe and effective use of Accutane.

The first barrier that these authors identified was the lack of awareness of the guideline, and as an example, they cite that 84 percent of practicing internists and family practitioners are not aware of the United States Preventative Services Task Force. These are the recommendations that put in place screening and other strategies for the health maintenance of patients.

They also, as a contrast, cite the National Heart, Lung and Blood Institute guidelines for the management of asthma, of which 99 percent of the practicing physicians are aware of these guidelines. So, there is probably some lesson to be learned here as to how one gets out at a 99 percent penetration rate, yet another one, which was well touted, only has relatively little awareness on the part of practicing physicians.

The second major barrier they cite is lack of familiarity. They are aware of the guidelines. They just don't know what it says. They cite that 89 percent of practicing physicians are unaware of the American College

of Physicians exercise stress testing guidelines.

The third major barrier is lack of agreement. For this they cite that over 90 percent of practicing pediatricians disagree with the American Academy of Pediatrics ribavirin recommendations. So, they are aware of the recommendations, they're familiar with the recommendations, they don't agree with the recommendations. A significant barrier to implementation, I would say.

The fourth major barrier is lack of outcome expectancies. So, they're aware of it, they know what it says, they believe what it says, but they don't think it really is going to make a difference. For this they cite that 90 percent of the physicians think that the alcohol abuse prevention guidelines, even if they're followed, won't really make a difference.

The fifth one was the inertia of previous practice, and this was a very interesting one. About two-thirds of practicing neonatologists, pediatricians don't abide by the infant sleeping position guidelines to prevent the occurrence of sudden infant death syndrome. This is probably due to the fact that the recommendations seem to change relatively frequently. I think we can all remember that the lay press has picked up on this recommendation, saying that a child should be positioned on its stomach, at a 45 degree angle, on its back. Conflicting

recommendations I think leads to inertia and lack of adherence to the most recent one.

Finally, external barriers, such as inconvenience, confusing, time-consuming, or fundamentally that the physician doesn't think they can follow the guideline is an important consideration, especially with regard to the risk management strategies.

So, I'll close by saying, with knowledge of these barriers, do they apply to Accutane? I thank you for taking up this important issue. As you hear the data on Accutane, consider some of these barriers and how they may apply to the risk management options that we'll be presenting to you.

DR. BERGFELD: Thank you very much.

We're now going to move and segue into the next part of the morning's program, and that is the subject of the Accutane pregnancy prevention program. Our first presenter is Dr. Jonathan Wilkin, who will present on Accutane clinical background, regulatory history.

DR. WILKIN: During the next two days we will be discussing Accutane, which is isotretinoin. We should keep in mind during these two days that Accutane is uniquely effective for severe cystic acne, a mutilating, scarring condition that can severely compromise the quality of life. Accutane is also a potent teratogen, which has

attracted significant public interest and has been the focus of multiple advisory committee meetings, especially to consider the issue of pregnancy prevention. There is also an uncertain relationship with associated psychiatric events. Thus, it is timely that the committee considers the Accutane issues, since the sponsor proposes to introduce a new formulation.

Accutane was approved in May of 1982 with a pregnancy category X. The labeling described the risk of teratogenicity and contraindications, warnings, and precautions. A patient information brochure also contained warnings about avoiding pregnancy.

In 1983 came the first report of infant malformation. The sponsor distributed red stickers to pharmacies with further warnings. There were labeling changes. The first Dear Doctor letter was sent, and in the same year a second Dear Doctor letter was sent with additional information about the reported cases.

In 1984 came more labeling changes, a third Dear Doctor letter, and an advisory committee meeting that addressed monitoring for pregnancy. From 1984 to 1988 Roche issued seven Dear Doctor letters. In 1988, at an advisory committee meeting, Roche introduced the concept of the Accutane pregnancy prevention program.

There are some characteristic malformations

which occur when the infant is exposed in utero to Accutane. Microtia, anotia, micrognathia, conotruncal heart defects, aortic arch abnormalities, thymic ectopia/aplasia, cerebellar vermis agenesis, neuronal migration abnormalities, bones of the central face can be abnormal. There is no debate about the teratogenicity of Accutane. It occurs in approximately one in four exposed pregnancies. The issue really is how to prevent exposed pregnancies.

One of the cornerstones of pregnancy prevention for many patients is hormonal contraception. There have been disturbing reports of pregnancies occurring during use of both hormonal contraception and isotretinoin. There have been spontaneous marketing reports of hormonal contraception failure, not just oral contraceptives but implantable and injectable hormonal contraceptives as well. Pastuszak and Koren reported several additional cases of oral contraceptive failure, and then there is the Dai article in the Journal of the American Academy of Dermatology that provides additional information.

In Dai's article, isotretinoin-exposed pregnancy reports in the United States voluntarily submitted to Hoffmann-LaRoche from September 1982 to July 1989 were reviewed. The method of contraception was known for only 264 of the 433 patients who conceived. Over 16

percent of these women who became pregnant, ages 14 to 29 years, identified oral contraceptive as the method.

The only pre-2000 published study to investigate a potential isotretinoin interaction with oral contraceptives was by Orme, and it's actually reported in two locations. There is a briefer presentation that only mentions 9 patients and has very little detail, and it's found in 1984 in the Lancet. There's a 1983 version in Retinoid Therapy, edited by Cunliffe and Miller, which mentions 10 patients and has much more detail.

There were 10 women ages 19 to 29 years. They were taking six different oral contraceptives, long-term, and after a control cycle, isotretinoin 0.5 milligram per kilogram per day was introduced. I would point out that this is the lowest recommended dose and the upper end, the highest recommended dose is four times this amount.

In 2 of the patients the plasma levels of the oral contraceptive hormones decreased on isotretinoin, and in 1 patient there was a spike of the plasma progesterone to 2,300 picograms per ml. This was captured on day 12 through 15, which may not have actually captured the peak progesterone. If that signal is discounted then the 0 out out of 10 would rule out at the upper 95 percent confidence limit an interaction in more than 26 percent of the population. If interpreted as a signal, then the upper 95

percent confidence limit would be 44.5 percent.

So, this led to a labeling addition, July 13, 1994, which emphasized the need to use two reliable forms of contraception simultaneously. So, if hormonal is chosen, add a barrier method.

Because the FDA continues to receive reports of pregnancies coded as compliant with hormonal contraceptives, the labeling was further strengthened in May to include the following statements: "Any birth control method can fail. It is critically important that women of childbearing potential use two effective forms of contraception simultaneously, even when one of the forms is a hormonal contraceptive method."

There have been reports of pregnancy from women who have used oral contraceptives as well as injectable and implantable contraceptive products. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane.

Now, because today we have low estrogen oral contraceptives, progestin-only contraceptives, and a wide variety of progestational agents, the sponsor has ongoing studies to more thoroughly investigate a potential isotretinoin-hormonal contraceptive interaction, and we'll be discussing this tomorrow afternoon in the context of the new formulation.

Now, later this morning and this afternoon the committee will be considering the pregnancy prevention program, and I would emphasize that it is a voluntary program and there are several voluntary components to it. It's voluntary in its use by physicians, and whether patients choose to participate in the survey, which is conducted by the Slone Epidemiology Unit of Boston University School of Medicine, commissioned by Roche, and directed by Dr. Allen Mitchell, is also voluntary.

Dr. Mitchell's December 1997 report on the Slone survey indicates that 23 percent of the women did not report signing a consent form, which is a component of the voluntary pregnancy prevention program. 25 percent did not report having a pregnancy test before starting Accutane, also a component of the voluntary pregnancy prevention program. 33 percent did not report postponing the start of Accutane until the pregnancy test result was known, also a component of the voluntary program. And 43 percent did not report postponing the start of Accutane until their next menstrual period, also a component of the voluntary pregnancy prevention program.

In Dr. Mitchell's 1995 New England Journal of Medicine article, he points out that the women who did not enroll were more likely to be noncompliant. I think the article is in the sponsor's briefing document, if the

committee would like to review it further.

Tomorrow we'll be discussing the details of the association of psychiatric disorders with Accutane. The FDA has received postmarketing reports of associated psychiatric events, including depression and suicide. We also know of dose-dependent psychiatric events occurring with vitamin A, and there are reports in the literature of the association between psychiatric events and isotretinoin, such as this article from the NIH investigators.

Now, this article comes from the NIH group. Actually the title of the article is "Acute Depression from Isotretinoin." 7 of 700 patients in trials at the NIH who have diagnoses of acne, psoriasis, and basal cell carcinoma had an onset of depression on Accutane. The patients were older than the adolescent years, at ages 22 to 47 years, and a mean of 32 years. Importantly, the depression resolved within 7 days after discontinuing isotretinoin, which is consistent with the pharmacokinetics of isotretinoin.

Based on these reports, the following was added to labeling on February 24, 1998. "Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be insufficient. Further evaluation may be

necessary. No mechanism of action has been established for these events."

This is from something we probably all remember from college, Strunk and White, Elements of Style. What Strunk and White say is, save the auxiliaries, which includes the word "may" for situations involving real uncertainty. Although there is real uncertainty about isotretinoin causing psychiatric events, it is prudent that physicians act as if it does until we have more information.

Now, about the same time as this labeling change for psychiatric events, the sponsor was running this advertisement, and on the next slide the marked paragraph will be magnified so that you can read it.

The Roche advertisement for Accutane states that "effective treatment of severe recalcitrant nodular acne minimizes progressive physical scarring, as well as negative psychosocial effects such as depression and poor self image."

A warning letter was sent to Roche on March 5, 1998, which stated in part that statements and suggestions in Roche's promotional materials that Accutane therapy will minimize or improve the patient's psychological status, including depression, are false or misleading and promote an unapproved use.

Now, before closing this introduction, it is important to emphasize the uniquely effective nature of Accutane. You can see from the before and after slides here that Accutane can eliminate cystic acne, a mutilating, scarring condition, as no other treatment can.

This is a recent advertisement for Accutane, and the caption says, "Nine months after one course of Accutane," and of course, what it's speaking to is the remission can be permanent, even in the severe cystic acne. Of course, it can also be permanent in some of the lesser grades of acne, and this is one of the reasons for off-label use.

Not only can Accutane induce remission, unlike any other therapy, it is also more effective in control than any other therapy. Regardless what other therapy this young man is on, Accutane would almost certainly be more effective. I don't know if anyone can read this in the back, but it says, "Can your son's acne products do this?" Such campaigns as this directed to parents may serve to increase demand, even though Accutane is not specifically mentioned in this advertisement.

In summary, we should keep in mind that Accutane is uniquely effective for severe cystic acne. Accutane is a potent teratogen used in otherwise healthy teenagers and young adults. There is minimal evidence to

exclude a hormonal contraceptive-isotretinoin interaction. There is substantial evidence of incomplete use of the voluntary pregnancy prevention program. Infants continue to be born with isotretinoin-induced malformations. These aspects will be considered today.

Tomorrow we'll consider the relationship with the psychiatric disorders, which we believe remains uncertain. Finally, the sponsor is proposing a new isotretinoin formulation, which we'll discuss tomorrow afternoon.

DR. BERGFELD: Thank you, Jon.

The next presenter, then, is Dr. Amarilys Vega, who is going to present on pregnancy prevention program, postmarketing drug risk assessment.

DR. VEGA: The regulatory history of Accutane, as previously described by Dr. Wilkin, clearly demonstrates that a lot of effort has been put out into communicating to health care professionals and the general public the risks of teratogenicity associated with in utero exposure to Accutane. Accutane was initially labeled as a pregnancy category X and, as he already showed, has been intensely labeled for its teratogenicity. Patient and physician educational materials also contain lots of information about avoiding pregnancy.

In 1983 further labeling changes were made, and

as we continued to receive further information, Dear Doctor letters first, second, went out. The sponsor also distributed red stickers to pharmacies with further warnings.

More labeling changes were done in 1984 followed by the third Dear Doctor letter. And between 1984 and 1988, seven Dear Doctor letters were issued, all of these a reflection of the intense efforts that the company and the agency have been putting on to communicate the risk of teratogenicity to the public and health care professionals. This series of events culminated in the 1988 advisory committee, in which Roche introduced the novel approach of the pregnancy prevention program.

The main objective of this program is to prevent pregnancy exposure among women exposed to Accutane. The Accutane pregnancy prevention program consists of warning labels on the product package, informed consent form for female patients, warnings on the product package, and a PPP kit for prescribers. Numerous patient and physician educational efforts have been undertaken. The Accutane tracking study and the patient enrollment survey also form part of this pregnancy prevention program.

The label contains a boxed warning which describes a series of characteristics females of childbearing potential should have in order to qualify for

treatment with Accutane. It also emphasizes the importance of pregnancy testing before starting treatment and during therapy, as well as the need to use two reliable methods of contraception, starting one month before therapy, during therapy, and one month after treatment. It also contains instructions to begin treatment on the second and third day of the next menstrual period.

The boxed warning also contains specific information about when to start taking the medication, which should be within the specified period of time. It mentions that a negative pregnancy test should be obtained within a week from starting therapy. The prescription should not exceed a one-month supply of Accutane, and that female patients of childbearing potential must have monthly pregnancy testing and monthly contraceptive counseling.

An informed consent for female patients supplied by Roche reiterates the teratogenic risk of in utero exposure to the drug and emphasizes pregnancy prevention practices required for the safe use of Accutane. Roche has also introduced a blister package with a "Do Not Get Pregnant" sign on it.

A very important part of Accutane PPP is the pregnancy prevention program kit for prescribers, which contains pregnancy counseling materials, patient information brochures, information on the patient referral

program, and a toll-free number for patients and health care providers. The sponsor has also embarked on many other educational efforts, such as CME courses and training videos for residency programs. All of these represent a tremendous effort by the sponsor to educate patients and health care providers about the teratogenic risks of Accutane.

The Accutane tracking study and patient enrollment surveys are integral parts of the Accutane pregnancy prevention program. The Accutane tracking study evaluates physicians' usage of the pregnancy prevention program kit and other core components of the PPP.

The patient enrollment survey, the Slone survey, is an independent follow-up survey conducted by the Slone Epidemiology Unit of the Boston University School of Public Health.

The Accutane tracking study is a telephone survey which includes dermatologists and primary care physicians. The purpose of this survey is to determine physicians' usage of the pregnancy prevention program components. The major limitation of the study is that it tracks physicians' perceptions of their use of the program materials rather than the actual use of them.

The Slone is a voluntary survey of women treated with Accutane and it seeks to measure patients'

knowledge about Accutane's teratogenicity, compliance with PPP components, pregnancy exposure rates among survey enrollees, and to characterize Accutane female users' profile, including some of the risk factors for pregnancy exposure.

It has been estimated that the Slone survey captures 30 to 40 percent of all women treated with Accutane. This represents a real problem. What goes on with the remaining 60 to 70 percent of these women no one knows for sure.

To measure the impact of the Accutane pregnancy prevention program of the occurrence of pregnancy exposures, we have available the following tools. The Slone survey, which, as I mentioned, is voluntary and has incomplete capture of Accutane female users. The Accutane tracking study, which captures physicians' perceptions of PPP kit usage, and spontaneous case reports with their numerous limitations. These, as you may see, are less than ideal tools to monitor the impact of a program of tremendous public health importance.

Accutane pregnancy prevention program has by no means been a static program. It has been fine-tuned by Roche through its lifetime. Nevertheless, both Roche and FDA have evaluated this program's performance and concluded that there are specific areas of the program which need to

be strengthened.

These areas of concern may be summarized under the following headings: the patterns of drug use, the performance characteristics of the pregnancy prevention programs as described by the Slone survey, and the Accutane tracking study, and case reports data.

This slide shows the estimated number of patients treated with Accutane by year from 1982 to 1999 using two different sources of drug use data and different methodologies to estimate the number of patients exposed to the drug. The line on top, the one that has the arrow and says NDC, is however, a more accurate representation of the total number of patients treated with Accutane. The conclusion, however, is the same regardless of the method used to estimate these numbers.

Since the early 1990s, the number of patients treated with Accutane has really increased. The change from 1992 to 1999 represents a little above a 200 percent increase. About 50 percent of Accutane users are females. 85 to 90 percent of those females are women in their childbearing years. This is between 15 and 44 years. Among women 15 to 44, 75 to 80 percent are below age 30, the age of peak fertility.

If we take the estimated number of females 15 to 44 treated with Accutane in 1999 and divide it by the

estimated number of females of childbearing potential in the U.S. for the same year, the result is approximately 2.5 per 1,000 reproductive aged women in the U.S. were exposed to Accutane last year. This is a high exposure to a known human teratogen.

This is again to show the number of Accutane users by gender, and as I mentioned earlier, the male to female ratio is about 1 to 1, and it has remained fairly stable through time.

In summary, the use of Accutane in women approximates the use in men. Accutane use in women has increased over 200 percent between 1992 and 1999. 85 to 90 percent of women using Accutane are age 15 to 44. Among women 15 to 44, 80 percent of use is below age 30. All these figures indicate high levels of exposure to a known human teratogen during the peak years of fertility.

You'll be hearing a lot more in-depth description of the Slone data later on today by the experts, but we would like to highlight some important points.

As I mentioned early on, the Slone captures approximately 30 to 40 percent of all Auctane female users. We must keep in mind, however, that we don't know what goes on with the other 60 to 70 percent of these women. The following data describes characteristics of the subset of

women captured by the survey. Approximately 500,000 women have been enrolled in the Slone since its inception on January 1, 1989, and over 322,000 have completed follow-up information.

This slide describes the distribution of women enrolled in the Slone survey by pregnancy risk category. 40 percent of the enrollees reported to be sexually active. The majority used some kind of contraception. About 1 percent sexually active women were not using contraception. 57 percent report that they were not sexually active, and this represents a low level of sexual activity for age and raises additional questions about the other 60 to 70 percent of women not captured by the survey. About 4 percent reported they had hysterectomies, were post-menopausal, or their pregnancy risk category was unknown.

A group of concern is the group not reporting to be sexually active and not using birth control. We know the sexual activity status from being not sexually active to becoming sexually active may change overnight.

How are the women enrolled in the Slone survey and their physicians complying with core pregnancy prevention program elements? First, I should mention that these categories are not mutually exclusive.

23 Twenty-three percent did not report signing a consent form. 25 did not have a pregnancy test before

starting therapy. This is that no one checked if these women were pregnant before starting therapy with a known human teratogen. Unfortunately, it keeps getting worse. 33 percent started Auctane and did not wait for the results of the pregnancy test to document that they were not pregnant, and they proceeded to start taking Accutane.

Only 43 percent waited until the second or third day of their next menstrual period to start Accutane. 40 percent had no pregnancy test at all during treatment with Accutane.

These are unacceptable high percentages of physicians and patients not complying with core components of the pregnancy prevention program, all of them clearly described by Roche in all their materials for patients and physicians.

How are the remaining 60 to 70 percent of women and their physicians complying with the program? No one knows for sure, but we certainly know that this group is not doing well.

Data from the sponsor's most recent quarterly report to the agency shows that so far 958 pregnancies have been identified in the Slone survey. Of these, 644, or 67 percent, were elective terminations. 110 resulted in live births, and in 14 cases the outcome was unknown.

111 infants resulted from these pregnancies.

Of these, 60 infants were examined and had available medical records. Among these 60 infants, 8 had major congenital anomalies, for a 13 percent rate of congenital malformations. This is way below the 25 percent reported in the literature.

This table shows pregnancy rates among Slone survey enrollees from 1991 to 1998. These rates are based on voluntary self-reporting by survey participants, and they show a decline. We want to emphasize, however, that these are pregnancy reporting rates and do not necessarily represent the actual number of pregnancies occurring among Slone survey enrollees. If we apply those rates to the number of person-years contributed by women treated with Accutane in the U.S. for each of these years, the column on your right shows the number of pregnancies that would be estimated.

Based on these yearly estimates of pregnancy exposures, pregnancy reporting rates are decreasing, but the absolute number of pregnancies increases as a function of the expanding use of the drug, as I already showed you. We will come back to the issue of number of pregnancy exposures in a few moments.

In summary, pregnancies are still occurring. Substantial noncompliance with critical elements of the Accutane pregnancy prevention program is well documented.

Representativeness of the survey is unlikely.

As I mentioned before, the major limitation of the Accutane tracking study is that it tracks physicians' perceptions of their use of the program components rather than their actual use of them. This study showed that physicians do not use all the elements included in the kit because they feel it's adequate and sufficient, and they feel the pregnancy prevention program kit is inconvenient to them. The survey also suggests a high use of product brochure and a slight increase over time in the report of pregnancy testing and the use of the consent form.

Before embarking on a discussion of spontaneous case reports data, I would like to highlight two of the multiple limitations of case reports which are particularly important in this situation. Only a small percentage of adverse drug events are recognized and reported to the FDA. Under-reporting of adverse drug reactions is significant, and reporting of adverse drug events typically declines over the marketing history of a drug product.

This graph shows U.S. pregnancy reports received by the sponsor by outcome and year of therapy for 1982 to 1999. The four lines in this chart show number of pregnancy exposures total and by various pregnancy outcomes. The top one is the total number of pregnancy exposures reported. The second one in descending order is

the number of elective terminations. The third one are spontaneous abortions. And the last one is the line corresponding to the data on congenital anomalies.

We have plotted data until 1997 because of a lag time of approximately 3 to 4 years between year of therapy and the year when the report is filed. So, we have complete and fairly stable numbers until 1997 only.

Based on this graph, we may say that spontaneous case reports of pregnancy exposures to Accutane are still received by the sponsor and the agency. The number of case reports of congenital anomalies has remained constant over time in spite of the existence of a pregnancy prevention program. The majority of all these pregnancy exposures result in elective terminations. The absolute number of case reports of pregnancy exposures to Accutane is definitely not declining.

Data from the sponsor's most recent quarterly report to the agency shows that so far Roche has received 1,995 cases of pregnancy exposures to Accutane since approval. 70 percent of these occurred after the initiation of the Accutane pregnancy prevention program. 60 percent of these exposures resulted in elective terminations, 383 in live birth, and in 166 cases the outcome was unknown.

162 of these infants have congenital anomalies.

This is a rate of 42 percent of all live births. We know, however, that spontaneous case reports series are enriched by cases reporting the most serious outcomes. Thus, we know this reported rate is inflated by this bias in reporting.

The rates of congenital anomalies identified by the two different sources of data I have just presented --- this is the Slone survey and spontaneous case reports -- are distanced from the generally accepted rate of 25 percent described in the literature. The 42 percent is high because of the reporting bias, and the 13 percent is low because of under-ascertainment of pregnancy exposure in cases of congenital anomalies.

In summary, pregnancy exposures reported to Roche and FDA are not declining. 70 percent of all exposed pregnancies have been documented by Roche since the beginning of the Accutane pregnancy prevention program. Congenital anomalies continue to be reported to the sponsor and the agency. With the data at hand, it is not possible to reliably quantify the changes in the occurrence of pregnancy exposure to Accutane in the most recent years.

To get a ballpark number estimate of the potential pregnancy exposures to Accutane in a given year, we have developed the following model based on very conservative assumptions. Let me talk you through the

different steps.

Step number 1. We estimated the number of females 15 to 44 years treated with Accutane in 1999. For now, let's forget about the lower portion of this slide and let's concentrate on the top portion where we see the Slone and the perfect typical use. Let's talk about that part first.

In the second step, if we take the total number of females 15 to 44 years treated with Accutane in 1999, and assume that all the women exposed to Accutane follow the distribution of contraceptive use described by Slone, we will get an estimate of the total number of women using each method of contraception, and this includes those not using contraception.

In the following step, step number 3, we know that all contraceptive methods have failures. These failure rates vary according to how the specific methods are being used. Some people use the methods perfectly, follow all the instructions on the label, don't forget to take their contraceptives, and they have lower pregnancy rates than those who are not so cautious.

Then we apply these failure rates for perfect use and for typical use to the numbers that we obtain on step number 2. These will give us the estimated number of pregnancy exposures if all the women taking Accutane would

follow the distribution of oral contraceptives described by Slone, and if they had perfect or typical use, depending on their contraceptive methods.

The National Survey of Family Growth, which is the NSFG that you see on the lower circle -- now we can look at the lower part of the diagram -- is a nationally representative survey. Its main function is to collect data on factors affecting pregnancy and women's health. We obtained the distribution of contraceptive use followed by women in the general population from this survey, and we follow exactly the same steps that we follow as we did with the Slone distribution.

Based on contraceptive failure rates alone, we get numbers which are two to four times larger than those numbers obtained when we use pregnancy reporting rates from the Slone. I'm referring to these numbers up here. So, these are based on contraceptive failure rates only. These strongly suggest that pregnancies are being under-ascertained by the Slone survey. This bring us back to the self-reporting nature of the Slone survey. The true number is probably between these two models here. We need better means to enumerate pregnancy exposures.

How many pregnancy exposures to Accutane occurred in 1999? No one knows for sure. We know Accutane is a human teratogen, and that's why we have a pregnancy

prevention program in place. We do not have a reliable way to track pregnancy exposures to Accutane, and consequently we do not have a good way to monitor the public health impact of this program.

In conclusion, drug use of Accutane among women of childbearing potential is escalating. We have a real problem with compliance with core program components, and in spite of all the sponsor's and FDA efforts to communicate Accutane's teratogenic potential, there is still limited compliance with pregnancy testing before exposure, pregnancy testing during exposure, and the use of appropriate contraception.

Measures of pregnancy exposures and outcomes based on the Slone survey and spontaneous case reports are not representative of all female Accutane users. Because the enumeration of cases of exposure through this means is so poor, we are forced to rely on estimates. It would be much better if we had better means to accurately and completely enumerate cases. And finally, increasing numbers of women exposed to Accutane increases the absolute number of pregnancy exposures.

Thank you.

DR. BERGFELD: Thank you very much. Our next presenter then is Dr. Edward Lammer, medical geneticist, FDA consultant from Oakland, California, who will be

presenting on pregnancy exposures and teratogenicity.

DR. LAMMER: Thank you. I'm the Director of the Medical Genetics Program, the Craniofacial Center at Oakland Children's Hospital.

I've been present for the 1988, 1989, and 1990 meetings of this advisory committee, and it was interesting going back over this weekend and re-reading the transcripts from those three meetings. It's an interesting historical note.

I've been involved with tracking pregnancies exposed to Accutane since really 1984 when I worked for the Center for Disease Control and started these projects. Our projects are not terribly active currently, in part because I think we've pretty much defined this particular syndrome and what the risks are to women who use this drug during pregnancy and what happens to the babies afterward. My collaborator Jane Adams is also here, and she has expertise in the area of the central nervous system problems that these children have that may not be evident at birth.

I think one of the things to really emphasize here is that surveillance with major structural malformations really just hits the tip of the iceberg of the adverse effects that result from the use of this drug during pregnancy. I think I'll just start by running through very briefly the magnitude of risks that we've

identified from exposure to this drug and exactly briefly really what this phenotype looks like.

This is actually an old slide, but the results are pretty much the same now. That is, we've tracked now close to 200 pregnancies that we identified prospectively. That is, the mother using the Accutane drug and was reported and identified to us before any prenatal ultrasonography or other tests had been done that would indicate the status of the fetus, and the results are pretty much like this.

We lose to follow-up a small handful of these mothers. Some of them go on to have spontaneous abortions, and then from this population, when we were doing our active study, 77 of them were live born. The top three numbers are really what we call embryonic exposures; that is, women who used the drug in the first 60 days after conception. In fact, almost all the women used the drug between conception and day 45, so you can really think of it in that sense.

In addition, we've tracked probably 12 or 15 children I think now, where the exposure occurred in what we call the fetal period. That is, the mother did not start using the drug until more than 60 days after conception. There are problems among those children as well, but they are largely limited to problems affecting

the brain, and I'm not going to talk about them today.

So, if you can identify the pregnancies early enough -- and these are the first 65 that we identified before 13 weeks after the last menstrual period. That would be women who are still at risk at the time we ascertain them to have a spontaneous abortion. What we find is that of the first 65 pregnancies that we identified early enough to be able to measure risk for spontaneous abortion, 40 percent of those women had that adverse outcome. That's about 2.5 times the typical number that's used, which is about 15 percent for risk of spontaneous abortion among clinically recognized pregnancies, which these clearly all would be.

We tried at various times to do pathology evaluations on these aborted embryos but were really unsuccessful for that. The assumption, of course, is that many of these embryos are severely malformed, but we really don't know that that's the case.

Again, the absolute risk in our data for spontaneous abortions is 40 percent.

And then of the babies who are live born, we have evaluated them a number of times since birth. Usually I saw them in the first 2 years of life and then, with Dr. Adams, did a large developmental battery of tests at age 5, and then Dr. Adams has seen all these children again at age

10. So, we have a good picture longitudinally of what happens to these children, and the full range of adverse effects that can result from exposure to the drug, even from a relatively unbiased population.

One of the things we have noticed is that these babies have about a 300-gram difference in birth weight from our control group, and that difference is really not explained by intrauterine growth retardation. It's explained by prematurity. So, despite the fact that these exposures all occur only in the early part of the first trimester, about 16 percent of these pregnancies result in a delivery before 37 weeks of gestational age. That's clearly an excess. Most of these babies are born to Caucasian women for whom the risk of premature delivery is substantially below 16 percent.

These babies are not growth retarded, which is unusual for most known human teratogens. They do develop frequently postnatal growth retardation, but at least intrauterine growth retardation would be an extremely uncommon feature of this syndrome.

Now, you've heard Dr. Vega present a summary of what the absolute risk is for an infant to be born with a major malformation, and you can see in the pie chart here on the left that if you look at all of the pregnancies that we've tracked, that would be 77 where the exposures

occurred sometime between conception and day 60. 23 percent of those have at least one major malformation, and this is an extraordinarily high absolute risk, really comparable, in terms of environmental exposures, only to thalidomide or certain congenital infections. There is no other medication that poses an absolute risk anything remotely close to this, even medications used to treat cancer during pregnancy.

Now, if you take that group and subdivide them, all the risk appears in the women who continue to take the drug more than 15 days after conception. So, if the woman stops the drug before 15 days, the risk that she'd have a baby with a major malformation is really indistinguishable from background risk. So, all of the risk is really among women who continue to take this drug beyond 15 days, and that fits with the observed malformation pattern, which is one that suggests that this drug primarily affects cranial neural crest cells, which begin their migration and activity around 18 days after conception, and effects on the brain, which are undoubtedly due to a different mechanism other than an effect on cranial neural crest cells because the brain appears to be susceptible to the effects of this drug throughout the entire pregnancy, from our experience.

The phenotype is pretty straightforward. Brain

abnormalities, tragically, are by far and away the most common problem, even among babies who appear to be perfectly normal at birth. Effects on facial development are primarily on bones and cartilage of the face, the external ears, occasionally the palate, the mandible. But the ear structures are most commonly affected. The third most common abnormality would be heart defects, congenital heart defects, many of which are fatal. Thymic deficiency and hypoparathyroidism. That's basically the phenotype that we see. It's unusual to see problems in other parts of the body except among the most severely affected children.

Just to give you an idea how some of these, this is a baby is almost a complete absence of ear development. All there is is a little slit with a small piece of cartilage. This child has severe hydrocephalus, spent his entire life in a nursing home in Pennsylvania and died after several years.

This shows the typical hind brain abnormality. This is the brain stem, the two cerebellar hemispheres. This is a cyst filling the space between the cerebellar hemispheres, a malformation commonly known as the Dandy Walker anomaly. There are more children with Accutane embryopathy who have this malformation than any other cause that's ever been reported in the literature as a cause of a

Dandy Walker malformation.

This is just to emphasize the point that this drug causes much more than just major malformations of the brain. This is a section through the medulla, the hind brain. We see this structure right here that looks oval. That's an inferior olive, part of the tract related to controlling movement. That normally should have an undulated C-shaped appearance, and what we see here is just a globular bunch of nerve cells that completely lack the normal structure of this part of the hind brain. So, there are diffuse abnormalities throughout the brain.

Here's another good example. This big thing right here is a heterotopia, which is a collection of cells in the part of the brain where they should not be. This is the edge of a cut through a section of the cerebellum. This is a completely disorganized mass of cells that's composed of all the different cell types in this part of the brain, and they are completely disorganized and wil have absolutely no functional benefit and certainly will contribute to adverse effects in this child.

The point I'm really trying to make here is that the major malformations in the brain are really only a signal that there are more subtle problems that cannot be detected except really at autopsy, or through the studies that Dr. Adams has done that demonstrate that many of these

children who appear normal at birth -- in other words, they don't have obvious major malformations -- have deficits in full scale IQ scores and a number of specific learning problems that, if you want to hear from Dr. Adams, she could explain in much more detail than I can.

Here's an example of some of the craniofacial anomalies. This drug can completely inhibit formation of the ear so that there's no trace of any ear development whatsoever.

This is another characteristic ear malformation which, for reasons we don't understand well, is identical to the type of ear malformations induced by thalidomide. That is, you get formation of part of the ear derived from the first branchial arch, but complete inhibition of development of the parts of the ear that derive from the second branchial arch tissue.

That's really all I wanted to show this morning. The point really is that surveillance for major structural malformations really only hits the tip of the iceberg of the adverse effects of this drug when it's used during pregnancy. I think you saw the data from Dr. Mitchell's survey during this morning. During the era of the survey, they've identified 8 children with at least one major malformation from that survey. I personally am contacted by six to eight cases of children with major

malformations every year during the 1990s.

So, this problem is not one that's going away. I think if you go back and read the transcripts from the hearings from '88, '89 and '90, you'll see that in that era consultants to Hoffmann-LaRoche were falling all over themselves trying to justify that 70,000 women deserved to get prescriptions of this drug per year. You saw the data that since that time there are now over 200,000 new prescriptions per year in reproductive aged women. I don't see how this can really be justified. If you go back and read the transcripts, you'll see that Dr. Strauss, an eminent dermatologist from the university where I went to medical school, estimated only 10 years ago that he thought 70,000 new prescriptions per year in reproductive aged women seemed like it was right on the mark. Now we're being told that that number has hugely increased, at least a 200-fold increase, and that this number in the minds of some people seems like it's okay as well.

I think there's clearly a problem with over-prescribing, and I hope members of this committee will go back and read the transcripts from 10, 11 and 12 years ago, to see what was said at that time in terms of estimates of the number of reproductive aged women who ought to have severe enough acne to warrant being put on this drug. I think I'll stop there.

DR. BERGFELD: Thank you very much. Dr. Adams, would you like to add to the remarks of Dr. Lammer?

DR. ADAMS: I'm sorry. I'm certainly not prepared to show you any slides or anything, but I think my main comment would be that everyone has to keep in mind that there is a continuum of abnormal development caused by Accutane, and often the focus is strictly on congenital malformations which, as Dr. Lammer pointed out, is just one endpoint.

You have to remember the 40 percent who are naturally miscarried when the woman is on this drug during pregnancy.

You have to remember that when we talk about a 25 to 35 percent malformation rate, we are talking about 25 to 35 percent of the only 60 percent that make it to term.

And then you have to remember that the 25 percent malformation rate does not capture the functionally impaired children because there are many children with severe learning disabilities who do not have major malformations that were detectable at birth.

Thank you.

DR. BERGFELD: Thank you very much. It's now time for questions by the committee, and I would state that these would be clarification questions regarding the presenters' materials. If you're asking a question, if

you'd please present your name first so that they can record this with your question. Any questions from the committee members?

DR. ABEL: Elizabeth Abel. I just have one for Roche regarding the types of contraceptive recommendations. Does one have to be hormonal, or could two of the methods be non-hormonal?

MS. LEACH: My name is Eileen Leach.

The May 2000 label calls for two separate effective contraception to be used, one primary and one secondary.

DR. ABEL: So, it is not defined?

MS. LEACH: Yes. In fact, the primary contraception is listed in the patient brochures as well as in the informed consent.

DR. BERGFELD: Thank you.

Any other questions? Dr. King.

DR. KING: Dr. Lloyd King, Vanderbilt, Nashville.

I have a question for Dr. Lammer and Dr. Adams. It's unclear to me in your conversation whether there are an effects of hypervitaminosis A due to increased taking of multivtiamin during pregnancy and/or a lack of folic acid or other factors. Can you identify specifically the risks due to Accutane or what are these other factors that affect

the central nervous system? How are they enumerated? Is that a clear question?

DR. LAMMER: I'm a little unclear about your question. Folic acid has been shown to be beneficial in preventing neural tube defects, and to the best of my knowledge, there has only been one instance with a neural tube defect associated with exposure to retinoic acid. So, neural tube defects are not a characteristic central nervous system problem among infants whose mothers used this drug during pregnancy.

DR. KING: Then what about hypervitaminosis A?

DR. LAMMER: We interview all these mothers and ask them about their intake of vitamin A in terms of a supplement during pregnancy, and none of these mothers were taking a supplement of vitamin A along with their Accutane prescription, if that's your question.

DR. KING: That's the question.

Then a follow-up is the inference is that there was a pregnancy test prior to entering and then monthly. That would detect the population at risk. Is that your implication?

You were saying that the major risk was in the first 15-20 days, that if you knew prior to taking the drug and then with the follow-up test in 1 month, 4 weeks, that you would identify the population at risk. Is that

correct?

DR. LAMMER: No. My comment, Terry, really was only to delineate that there are differential periods of risk from exposure during the pregnancy. That was really all that I meant with that presentation.

DR. BERGFELD: Yes, Dr. Adams.

DR. ADAMS: Just to get to this issue of time of vulnerability, Dr. Lammer was intending to show that vulnerability begins at about day 14, 2 weeks post-conception. We know from the sample that there are people who had one pill who had abnormal babies because the exposure occurred during this period, and no, a monthly pregnancy test would not capture them. You would have a full day 14 to day 30 potential period of exposure in there that could occur for these women, and that would be a very high period of risk. So, the idea that monthly follow-ups for pregnancy for women on this drug would considerably reduce risk is just not the reality.

DR. BERGFELD: Thank you.

Yes.

DR. MILLS: I'm James Mills from the National Institutes of Health.

Dr. Vega, you presented data on pregnancy rates based on estimates of perfect and typical failure rates of contraceptives. I was a little confused about that in the

sense that are these based on a single method of contraception, or two methods, and based on what combination of failure rates?

DR. VEGA: That's a very good question. I should mention that for the Slone survey estimates we adjusted those pregnancy failure rates for the use of two or more methods of contraception because there's like about 200 possible combinations. It was impossible to factor all those in. So, we assumed that those using two methods or more were not at risk of pregnancy. That's why I said that we used very conservative assumptions. So, we basically eliminated those patients' risk to get pregnant.

DR. BERGFELD: Yes.

DR. JONES: I'm Ken Jones.

I'd like to address a question to Dr. Raczkowski, and it relates to educational programs to the public that you enumerated. One of those programs that you talked about was advertising. I would appreciate it if you could enlighten us about restrictions that are imposed on advertising regarding a drug that the FDA places upon a sponsor.

DR. RACZKOWSKI: The main thing with advertising is that the advertising materials have to represent a fair balance of both the benefits and the risks of the drug. So, in a nutshell, that's the primary

restriction that the FDA places, that the advertising materials have to represent a fair balance.

DR. JONES: And to further that, can you comment about the advertising for Accutane at the present time? For example, it does not seem to me that many of the advertisements that I have heard on such programs as Nickelodeon, which clearly are being directed towards children, I don't think you see the teratogenic effect of Accutane when you hear the advertisement on TV. Can you comment about that?

DR. RACZKOWSKI: I'm not familiar with the advertisements, and so I'd prefer not to comment.

DR. JONES: You haven't seen the advertisements?

DR. RACZKOWSKI: I'd prefer not to comment.

DR. JONES: Is there somebody that could comment about that for us, please?

DR. BERGFELD: Perhaps the Roche people would comment in the afternoon when they present.

Dr. Wilkin?

DR. WILKIN: That was going to be my suggestion. I personally don't watch Nickelodeon, so I don't know --

DR. JONES: I'm a pediatrician. I do.

(Laughter.)

DR. WILKIN: You do. Well, perhaps you could or later the folks from Roche could describe what that is. Does it actually mention the name Accutane? Because if it doesn't really mention the name Accutane, then it may not really be an advertisement that our drug advertisement folks would review.

DR. JONES: No, it does not specifically use the word Accutane, and I think that's an obfuscation, if you will, as far as this is concerned. And I think that it certainly should come under the jurisdiction of the FDA, whether the word Accutane is used or not because certainly the implication is there.

DR. BERGFELD: Thank you.

Yes?

DR. KODISH: Eric Kodish from Rainbow, Cleveland.

To take this discussion perhaps from the mass marketing level to the clinical bedside level, we think about informed consent as both a document and a process, and I heard some discussion about the document, but the document should not dominate the process, most people in ethics say. I'm wondering whether anyone has any data, information about the informed consent process itself.

DR. BERGFELD: Dr. Wilkin or Roche?

DR. WILKIN: Actually Dr. Mitchell might have

some information perhaps gleaned through the Slone survey on that point.

DR. MITCHELL: No, we don't have any specific process information currently collected in the survey.

DR. BERGFELD: Thank you. Dr. Moore?

DR. MOORE: I just had one more question about the advertising. Did I understand the presentation correctly, that any drugs that have a boxed warning are not allowed to have advertising which actually names the product? Was that correct? I think that was in Dr. Raczkowski's.

DR. RACZKOWSKI: The only restriction that a boxed warning places on advertising is that you cannot have so-called reminder ads, and those are the sort of ads where you might say the name of a product on a pen, without any other additional information, just the name of the product. That's called a reminder ad.

DR. BERGFELD: There was another question over here. Dr. Abel?

DR. ABEL: Yes. Could someone from Roche please describe further the Accutane tracking study, and how that is carried out to capture physicians' perceptions.

DR. BERGFELD: A representative from Roche, please?

DR. LEACH: Actually the Accutane tracking

survey is conducted by Roche. Twice a year we survey 100 dermatologists and 300 family practitioners. They are asked about their use of the pregnancy prevention program and we break it down by actual pieces of the pregnancy prevention program. They are also asked about their patients' perception of the pregnancy prevention program.

DR. BERGFELD: Dr. Anderson?

DR. JENNIFER ANDERSON: Dr. Jennifer Anderson from Boston.

I have a question actually for Dr. Lammer about the possibility of birth defects with other drugs that are used to treat acne, like antibiotics. Dr. Lammer, you said that the birth defect rate with Accutane was much higher than with any other drug, but I was wondering what the rates might be with, say, antibiotics, which are commonly used.

DR. LAMMER: Commonly used antibiotics are not teratogenic at all. The only example I can really come up with off the top --

DR. ANDERSON: I mean commonly used to treat acne.

DR. BERGFELD: Tetracycline, erythromycin.

DR. LAMMER: Right. Tetracycline, when it's used beyond the fifth month of pregnancy, can cause yellowing and mottling and other abnormalities of the

teeth. It's absolutely not teratogenic used in the first trimester.

What other antibiotics are of concern?

DR. ANDERSON: I'm sorry. I don't know the names of them but I just --

DR. BERGFELD: Erythromycin.

DR. LAMMER: Erythromycin is not teratogenic either. As a general principle, there would be very few antibiotics that have been demonstrated to be teratogenic, and this late-in-pregnancy effect from tetracycline is the only thing that really comes to mind.

DR. BERGFELD: Dr. Greene?

DR. GREENE: I had question for Dr. Honig, please. During your presentation you mentioned the issue of clinical practice guidelines promulgated by professional societies and whether they do or do not have a significant impact on the practitioners. Are you familiar with what practice guidelines the dermatology professional associations may have promulgated and what effect they have had on their physicians?

DR. HONIG: I can't speak to that. Perhaps Dr. Wilkin could address that as a dermatologist.

DR. WILKIN: The American Academy of Dermatology has a task force that from time to time publishes in the Journal of the American Academy of

Dermatology practice care guidelines. Typically these are fairly open kinds of guidelines that really are nondirective. They don't say use treatment A, B, or C. They simply list treatments that are available. They typically go down the list of safety monitoring, these sorts of things. I don't really recall the specifics for the acne guideline.

Dr. Bergfeld?

DR. BERGFELD: I'll remove myself as chair and respond as the past president of the American Academy of Dermatology. As Dr. Wilkin did say, these guidelines are rather global. However, in the mention of Accutane, there is mention of dosage and selected patient populations of recalcitrant acne. I don't think that we in any way survey our population of physicians to see their use, nor their adverse events. We have been totally dependent on Roche and all of your patient and physician education to assist us in that.

DR. GREENE: Just a follow-up then. I can understand that they may not specifically advocate for the use of one treatment or another, but do they say anything with respect to if you're going to use Accutane beyond what the indications are for it, then here's what you need to do to make sure that no one gets injured.

DR. BERGFELD: Yes, they do have some specifics

on what needs to be done for the adverse event problem of the fetal teratogenicity. Yes, they do have that. And they do specifically state for recalcitrant cystic acne.

Now, the question might also evolve too, do they use it for other things? And the answer would be, obviously yes.

Any other questions? Yes, doctor.

MR. LEVIN: Arthur Levin.

Dr. Lammer, you made a comparison to thalidomide for ear malformation. I just wonder, overall how would you sort of rank the risks of this drug compared to other drugs with known birth defect risks?

DR. LAMMER: That's an excellent question and one that has been discussed at previous meetings of this advisory committee, so I think it is well worth going over. The magnitude of risk that this drug poses is essentially unique. The only other medications that I'm aware of that have a magnitude of risk in this range, when they are used during pregnancy, is really thalidomide. Congenital rubella infection might have an attack rate as high as well, but that's an infectious agent.

In terms of medications, in terms of the magnitude of risk and the severity of the malformations, this drug is really unique. Brain abnormalities are actually not that common in thalidomide embryopathy, but

that may in part have been problems with identification and how those studies were done in that era.

In terms of the phenotypic features of the two syndromes, they're really also quite strikingly similar. Other than there were many more children with limb abnormalities identified in association with thalidomide exposure. But otherwise heart defects, ear abnormalities were both frequent in both of the conditions and really resemble each other in many ways.

DR. BERGFELD: Question, Dr. Malone?

DR. MALONE: Dr. Malone from MCP Hanneman.

If we know that this drug causes abnormalities in fetuses for the brain, what does it tell us about what would happen in adults? Would it cause any changes in brain in adults?

DR. BERGFELD: Is there anyone that can respond to that question? Dr. Adams again.

DR. ADAMS: The ability of Accutane to affect the developing brain has to do with particular events that are only present during early developmental stages. It is often the case, nevertheless, that agents that can affect the developing brain overlap very highly with agents that can affect the adult brain. But in this case the mechanisms through which it acts prenatally would not be expected to even be present in adulthood under normal

circumstances.

DR. MALONE: I guess I was thinking mainly of the psychiatric symptoms you may get with Accutane. I guess there is no way to tell at what level this drug could cause changes in adults, from what you've said?

DR. BERGFELD: I think we're going to hear at length tomorrow on that issue, unless there is a short answer to it.

Seeing none, then any other questions? Yes, Dr. Jones again.

DR. JONES: I'm not sure quite who to direct this question to, but it relates to that Accutane tracking study, as well as the PPP. I was really impressed to see that there are 200 primary care physicians that are being interviewed as far as this Accutane tracking study because it was more my impression that PPP and then the targeted PPP were focused almost exclusively on dermatologists, and that there were an awful lot of other physicians that would be prescribing Accutane who really were not being educated to the same extent that dermatologists were. Can somebody comment about that? I maybe completely wrong.

DR. ELLISON: Russell Ellison from Roche.

It's an excellent question. Since the launch of this product 18 years ago, Roche has confined its promotion entirely to dermatologists because of the need to

select patients with severe recalcitrant nodular acne. On the other hand, the drug has been available for 18 years. So, other practitioners will start to prescribe it, particularly those with an interest in skin conditions. So, we thought it was important to include people like that in the survey to get a larger idea what's going on.

The second point is with respect to the Accutane patients survey. Patients in the survey are treated by any kind of physician. It's not selected for the physician, if you will. I think the following slide might be useful.

Basically 85 percent of prescriptions are from dermatologists and 15 percent, as far as we can tell, are from primary care practitioners. As far as their access to information, we don't, as I said, call on them directly because we don't want to promote to them, but they have the entire labeling situation and so on, and the patient gets the instructions and the informed consent.

DR. BERGFELD: Could I ask an additional question, if I might? If you identify these primary care physicians, pediatricians who are using the drug by another tracking mechanism, that is, purchasing the drug, and who has written the prescription, is it then appropriate that you call on them to give them the physician educational materials?

DR. ELLISON: I think it's a very good point of discussion. We've taken the balance of not having contact with these people, to make sure that we're not promoting use in that segment of the practicing population. At the same time, we recognize that there certainly would be advantages in terms of educating them. We've gone further to identify those general practitioners that prescribe more than once or twice per year and, based on our further discussions with the agency, are anticipating being able to call on them as well as we roll out the new targeted pregnancy prevention program.

DR. BERGFELD: Thank you.

Dr. Woodcock?

DR. WOODCOCK: I have a clarification question, if I may. Dr. Lammer and Dr. Adams, I was a little bit confused by what you were saying about the timing of exposure and the rate of birth defects detected. I understood you to say exposure I suppose to one or more pills of Accutane during the first 15 days after conception. Can you explain that a little bit?

DR. LAMMER: No. I think the comment that Dr. Adams made concerning risks from even one or two capsules of this medication would all be in women who took those pills after day 15. Women who stopped using this drug before conception, or within the first 15 days after

conception, we've not been able to identify that they have an increased risk to have babies with malformations.

DR. WOODCOCK: And you're dating conception like a teratologist would, from actual conception, not from the first day of the last menstrual period?

DR. LAMMER: That's correct. When I speak in terms of days, I'm talking about the estimated date of conception is day 0.

DR. WOODCOCK: Thank you.

DR. BERGFELD: Any other questions? Yes, doctor.

DR. GREENHILL: Dr. Greenhill from Columbia University.

I wonder if any comments could be made by the Food and Drug Administration about a program or recommendations they might have given for the reapproval of thalidomide, which has occurred in the last several years, for the treatment of leprosy. Is there a similar or parallel program in terms of letters to doctors, black box inserts, or suggestions or recommendations that would guide physicians and protect pregnant mothers?

DR. BERGFELD: Thank you.

Is there an FDA respondent? Yes, Dr. Vega.

DR. VEGA: This is Dr. Vega.

There is a program called the STEPS program, or

the System for Thalidomide Education and Prescribing Safety. This program is a pregnancy prevention program in essence, and it has educational materials for physicians and patients, and it contains tracking of the pregnancy exposures, and so forth. So, there is another program out there trying to do the same thing.

DR. GREENHILL: Does it differ in any way from the current program with Accutane?

DR. VEGA: Yes, it is in several ways. To begin with, it's a mandatory program. Participation in that program is required to get the drug. So, that's, I think, the main difference from the Accutane pregnancy prevention program because the educational component is there and the tracking of the pregnancy exposures. But I think the main difference is in the nature of the requirement to participate to get in the program.

DR. BERGFELD: Dr. Greene?

DR. GREENE: But Dr. Vega, please correct me if I'm wrong, but the system of distribution for thalidomide is far more restrictive. Pharmacies must register to dispense it. Not any pharmacy can dispense it. And physicians must register to prescribe it. Not any physician can prescribe it. So, it is very different and much more restrictive than the distribution system for Accutane, right?

DR. VEGA: Yes, that's correct. It's more restricted and the nature, as I said, it's required. It's mandatory, and it involves decisions in pharmacies and patients. So, that's correct.

DR. MURPHY: This is Dr. Murphy.

I just wanted to say one thing to the committee. Dr. Vega is going to go over a variety of options after Roche presents, and I think it will be clear that there are a number of elements that we will ask you to look at.

DR. BERGFELD: Thank you.

Any other questions? Dr. Miller.

DR. MILLER: Dr. Vega, this is in follow-up on the thalidomide. What's been the history of reporting of adverse events since its approval, do you know? Do you have any data?

DR. VEGA: Specifically on the pregnancy exposures, are your referring to?

DR. MILLER: Pregnancy and then perhaps any other significant adverse events, when you're looking at the program you have to ensure that it's not used without care and restriction.

DR. VEGA: So, your question is if there has been any pregnancy exposures, any babies born with congenital anomalies since the approval of thalidomide.

The answer is no. So, we can get into more details about the nature of the population exposed to thalidomide versus the Accutane. That might answer some of the questions. For a short answer, it's no.

DR. BERGFELD: For perspective, though, that program is how old?

DR. VEGA: June 1998, if I'm not mistaken.

DR. BERGFELD: Any other questions?

(No response.)

DR. BERGFELD: Seeing none, I'll declare a recess until 10:55, when we'll resume with Roche's presentation.

(Recess.)

DR. BERGFELD: Would everyone take their seats, please. We'd like to begin. We have a very full remainder of the morning, but before we proceed, Dr. Woodcock is going to do something for us on the advertising question that was asked earlier.

DR. WOODCOCK: Just to clarify the regulation of advertising. As I think was already stated, the reminder ads, where the name of the drug is just put up, are not permitted for drugs that have a black box warning. Health-seeking ads that simply mention a condition and talk about the condition and don't mention the name of a drug are not regulated as drug advertising. So, any promotion a

company would want to run about a particular disease condition that doesn't specifically point to any drug would not be subject to our regulation.

All other advertising, though, promotion that mentions a drug, would be subject to FDA rules and regulations, which require fair balance and disclosure of warning.

DR. BERGFELD: Could you then respond to the Nickelodeon ad or topic suggestion that was mentioned earlier? Who presented that? Dr. Jones, do you want to re-present that to Dr. Woodcock?

DR. JONES: I think you've answered my question, actually. I was asking specifically related to advertisements that, in fact, did not mention the drug. I assumed, therefore, that the reason the drug was not mentioned was to avoid having to talk about the teratogenic effect of the drug, and I'm sure other complications as well. And I think you've answered that and I appreciate it. Thank you.

DR. BERGFELD: Thank you, then.

Dr. Lammer?

DR. LAMMER: This kind of advertising may fit within the legal definition of what FDA allows, but I'd like to just read briefly from the presentation of Dr. Cunningham from Roche in 1989. I'm reading from the

transcript of the hearing of this committee on page 86 from 1989. "The advertising you've seen is rather dramatically focused on contraindication and proper usage of pregnancy prevention. It is not focused on usage. The two ads you've seen" -- these were ads for dermatologists -- "are representative of the type of advertising you will see in the future."

I'd like to ask whether the type of advertising that Dr. Jones brought up, which doesn't mention Accutane, but does have Roche's name and suggests and urges people to seek treatment for their acne or whatever, to me seems inconsistent with the company's previous statements of the type of advertising that they anticipated using in the future.

DR. BERGFELD: Yes, if you'll respond, please, Dr. Woodcock.

DR. WOODCOCK: Yes. I wasn't commenting on the consistency of advertising with previous commitments or whatever. I was simply saying the legal framework permits such health-seeking ads, and you see them for a wide variety of conditions. Cholesterol lowering, all sorts of things. There are these types of ads that are out there.

DR. BERGFELD: All right, I think we can then move on. The Roche presentation will be introduced by Dr. Russell Ellison.

DR. ELLISON: Dr. Bergfeld, members of the advisory committee and FDA, Hoffmann-LaRoche is pleased to be able to discuss how to improve the public health profile of this very important medication. I'm the Chief Medical Officer and Vice President of Medical Affairs of Roche Laboratories and I'd like to introduce our presentation.

As from the FDA briefing document, we all recognize the Accutane is uniquely and highly effective in the most severe form of acne which if not adequately treated, causes significant and often permanent disfigurement. At the same time, which I think Dr. Lammer has taken us through, Accutane is a very potent teratogen.

It was introduced in the U.S. in 1982 for severe recalcitrant nodular acne. Since that time about 5 million patients have been treated in the U.S. and 12 million worldwide. As FDA has pointed out, and we agree, use has been increasing since 1991.

We introduced the pregnancy prevention program that you've heard about in 1988. It was modified in 1989, based on data received in the Slone tracking survey to improve it, to prevent fetal exposure by preventing pregnancy.

We believe that from the data in the survey and other supportive data that the pregnancy rate is declining. We believe that the pregnancy rate in women on Accutane is

about 80 to 90 percent less than normal contraceptive use. We believe that given the pregnancy rate observed in our survey, that for every 1,000 women treated with Accutane pregnancy has not occurred in about 997.

The Accutane survey was introduced in 1989 as a risk assessment and risk monitoring tool of this program. Since that time, half a million women have been enrolled in the survey. The yearly enrollment has doubled since 1989. We believe that available data, from which you could compare the user population and the population in the Slone, supports the idea that the survey might be reasonably representative of the Accutane-treated population.

However, while these data would indicate that an individual's risk of pregnancy is decreasing, the total public health burden has not. That is, the absolute number of exposed pregnancies has not decreased. We believe the absolute goal is the prevention of pregnancy. We believe the first step along this goal is that the pregnancy rate must decline faster relative to use.

Our goal is the optimal program to further prevent pregnancies, balancing the likelihood of success, the risk of compromising current success for the vast majority of women who do not become pregnant while taking Accutane, and the risk of denying treatment to patients who

would not become pregnant.

We did launch this year a targeted pregnancy prevention program after discussions with FDA which specifically addresses the behaviors leading to pregnancies in women on Accutane.

Our presentation, after this very brief introduction, will start with a brief presentation by Dr. Guy Webster, Vice Chairman, Department of Dermatology at Jefferson Medical College, who will put the clinical benefits into context of real patients. Subsequently Dr. John LaFlore, our Vice President of Drug Safety and Risk Management at Roche Laboratories, will have a brief discussion about epidemiology, and he's going to shorten his presentation to focus entirely on the issue of pregnancies, as much as I think we're all agreed that use has increased. With respect to risk assessment and risk monitoring, Dr. Allen Mitchell will take us through a detailed discussion of the findings from the Slone survey. Subsequently Eileen Leach, whom you've already met, will discuss the details of the new targeted pregnancy prevention program based on what we've learned to further reduce pregnancies. And I will close with a brief discussion of other risk management options.

Thank you. Dr. Webster?

DR. WEBSTER: Madam Chairwoman, members of the

committee, guests. I'm the Vice President of Dermatology at Jefferson Medical College in Philadelphia, and for over 20 years I've been studying the pathogenesis of acne, and for the past 10 I've been treating it. I'm pleased to be here to present the benefits of Accutane to you.

This woman has been treated with maximal medical therapy already, short of Accutane. She has been given topical antibiotics, topical retinoids, oral antibiotics, and for her this is a good day. She still has nodules on her jaw. They're forming scars, and her life is really dominated by her severe disease. She needs Accutane. Nothing else will do it.

When a patient is treated for acne, they typically walk up the staircase of different treatments, starting with topical therapy, some over the counter, like benzoyl peroxide, progress to oral antibiotics, the tetracyclines, erythromycins, and then maybe the combination of oral and topical drugs such as topical retinoic acid and minocycline. A large number of patients still aren't better, still have resistant nodular scarring acne, and these are the people that should be put on Accutane.

This fellow is in high school. He's on maximal non-Accutane therapy, and he has devastating disfiguring disease. Picture going to school looking like this every

day. Picture looking at this in the mirror every day. It's pretty tough. This is his back. He hasn't yet been treated with Accutane and he has huge, disfiguring scars that will be with him for life.

The psychosocial effects of acne can't be minimized. First, it's a long-lasting disease. This is not the drugstore grade acne where a little of Clearasil makes it go away. This starts in the early teens and can last into the 30s, and it's not something that the patient can just ignore and put a little cover-up on. They become anxious and depressed. This is at a time when their personality is being formed and they have all the troubles every teenager has, plus they have acne. A lot of them become withdrawn and anxious and depressed.

All dermatology patients have been shown to have a higher prevalence of psychiatric disorders, and acne is no exception. They are more angry, they are more anxious, and they tend to do relatively badly in interpersonal situations.

Isotretinoin is a unique drug for treating acne because it addresses all of the pathogenic limbs that make the acne lesions form. It corrects the older pattern of follicular keratinization that forms the blackhead, behind which sebum backs up and P. acnes grows. It turns down the sebaceous gland activity so that sebum isn't produced and

there is no nutrition for the organism, Proprionibacterium acnes, that lives in the follicle and is the target for the inflammatory response. And finally, it's directly anti-inflammatory, cooling off lesions that have formed before treatment and reducing the chance of scarring.

This is what Accutane can do. This patient had had all the appropriate medical therapy before, short of Accutane, and finally became treated with it. He had inflamed nodules that were scarring on his chest. You can see what his chest looks like after treatment. This is his back. His back is more obviously scarred. He didn't get Accutane in time, but he clearly has had a remarkable change in the quality of his disease.

I apologize for the quality of these pictures. They were sent in by patients who were pleased with how they did. You can see on August 24th, she had big scarring nodules on her face, forehead and nose, and by December 2nd she was, for all intents and purposes, clear.

The same with this woman. Early in November she had nodular acne. Treatment was started. She had a little bit of irritation and flare. Her face is a little redder. By Christmas she has some irritation and fewer nodules, and by March there is nothing that you can see in the picture. This is a dramatic effect for patients who have been treated with everything else.

You can imagine how anxious patients are. It's been measured. Studies have shown that patients who are treated with isotretinoin do much better following treatment in a wide variety of psychological measurements, including anxiety and depression.

So, to sum up, isotretinoin is a unique drug. It's one that we cannot do without in dermatology. It gives a lasting response in disfiguring disease. It gives this response in a short duration of treatment, 4 to 6 months, and the long-term improvement in self-esteem and function is clear.

Thank you.

DR. LaFLORE: Good morning, Madam Chairwoman, advisory committee. My name is John LaFlore, Vice President, Drug Safety and Risk Management for Hoffmann-LaRoche.

As Dr. Ellison pointed out earlier in his introduction, the purpose of this section is to provide you with a basis for overall current patterns of Accutane use, as well as provide you with a context for the pregnancy prevention program, which will address risk assessment, and that will be addressed by Dr. Allen Mitchell, and risk management would be addressed by Ms. Eileen Leach following this presentation.

Also as Dr. Ellison mentioned, since we all

agreed that basically there is an increased use in Accutane over all the past years, some portions of this particular presentation have been shortened in order to save time for the other issues.

First of all, even though the use of Accutane has increased over the years, it does not imply that there has been an increased use outside the labeled indication. Though the use is increasing, pregnancy rates are basically declining, and absolute numbers of pregnancy reports have remained stable throughout the duration and life history of this drug. The overall pregnancy rate you see from the Slone survey is 2.8 per 1,000, and this is supported by additional international and other data which gives approximately the same rates.

In 1991, in cooperation with the FDA, Roche developed and agreed upon a set method for calculating overall use of Accutane. Within that method, we decided there were three parameters that would be adequate to give us a pretty significant estimate of what the overall use would be. The first one had to deal with the retail prescriptions directly from pharmacies themselves. The second was the third party payment tracking, and this was obtained from pharmacy records.

Now, the estimates then are adjusted to the Roche factory shipments, and this was allowed to give us a

definite increased look and a specific amount of estimates at that time. These data, keep in mind, were patient-based and not physician-based, as with IMS data.

This graph shows again, while the use of Accutane has increased over time, that both male and female use has increased at about the same rate, and toward the end they are actually approximately equal.

Now I'd like to move directly into the discussion regarding pregnancy. Again, while the use of Accutane has increased, pregnancy rates, as you can see according to this map, have declined. The number of reported pregnancies has remained basically stable. This takes into account both the spontaneous reports, as well as reports from the Accutane survey conducted by the Slone Epidemiology Unit at Boston University.

Now, with regards to receiving reports of pregnancies, there are two sources that we are primarily using.

One was the Accutane survey by the Slone Epidemiology Unit. It's important to keep in mind that this is solicited information and it contains a defined denominator. And it's this particular data source whereby we generate pregnancy rates. Of the one-half million women enrolled in this survey, greater than 80 percent have responded since the program began.

The second source of information of reports of pregnancy are obtained through the spontaneous reporting system, and these reports are received directly by Roche. Reports are also received from the agency, and also reports are received from the Centers for Disease Control, and those reports are also considered spontaneous, unsolicited reports.

Now, one might expect that pregnancy reports are decreasing since reporting of adverse events generally decrease over the time and the life of the product in terms of most drugs. However, as this graph shows, the spontaneous reports for Accutane has not decreased. However, the pregnancy reports from '91 to '98, the most completed data, show that they're being stable. This would suggest that there is no decline in the reporting of pregnancy rates.

One might then ask, does the Accutane survey with the defined denominator represent the actual user population? The proportional distribution of age in the Accutane survey is similar in the Accutane users' general population. If anything the survey over-represents the high risk group of 20 to 29-year-olds, those patients who are most likely at risk to become pregnant. Later Dr. Mitchell will go into more details with regard to the Accutane surrey.