TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

JOINT ADVISORY COMMITTEES

DERMATOLOGIC DRUGS ADVISORY COMMITTEE

FERTILITY AND MATERNAL HEALTH DRUGS ADVISORY COMMITTEE

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Monday, May 21, 1990

Conference Rooms D & E
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5600 Fishers Lane
Rockville, Maryland

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P R O C E E D I N G S

DR. LUMPKIN: Ladies and gentlemen, good morning. My name is Larry Lumpkin. I am the Director of the Division of Anti-Infective Drug Products, here at the FDA. The evaluation of dermatologic drug products comes under the purview of my Division and that is why I am happy to be here today and to welcome you to this Advisory Committee hearing.

As you are well aware, we have two different products that are on the agenda today. The first one is tretinoin emollient cream, NDA 19-963. The second one is Accutane, NDA 18-662.

Just to get some of the logistics straight from the beginning here, this morning the plan is that for the first hour, from 8:05-9:05, the open public hearing will be for both drugs. So if there is anyone from the public that wishes to make statements relative to either of those drugs, that is the appropriate time period for that to be done. After that we will go into a Committee discussion on tretinoin emollient cream. The issues for tretinoin emollient cream are only relative to the Dermatologic Advisory Committee and will be handled by the Dermatologic Advisory Committee alone, headed by Dr. Schroeter.

Following that discussion and the coffee break, we will go into the discussion of Accutane. As you are aware, we have a joint advisory committee set up to discuss that

topic. It will be a joint committee discussion between the Dermatologic Drugs Advisory Committee and the Fertility and Maternal Health Drugs Advisory Committee. That discussion will be co-chaired by the chair of both of those committees, Dr. Schroeter and Dr. Hulka.

As these committees have not met together in this format and as we have some new members on the committees, prior to starting the open public hearing, I would like to ask each of the committee members to simply introduce themselves and tell us where they are from so that they will get to know each other at the very beginning. If I could start on the other side, with the Fertility and Maternal Health Advisory Committee?

DR. BARBO: Dorothy Barbo, Philadelphia.

DR. DAVIDSON: Ezra Davidson, from Los Angeles.

DR. HANEY: Cap Haney, from Durham, North Carolina.

DR. MCKAY: Susan McKay, from Laramie, Wyoming.

DR. NIEBYL: Jennifer Niebyl, Iowa City, Iowa.

DR. ROY: Subir Roy, Los Angeles.

DR. SCHLESSELMAN: Jim Schlesselman, Bethesda, Maryland.

DR. WENTZ: Anne Colston Wentz, Chicago.

DR. HULKA: Barbara Hulka, from the University of North Carolina at Chapel Hill.

DR. LUMPKIN: And the dermatologic group?

of interest: It has been determined that all reported interests in firms regulated by the Center for Drug Evaluation Research which have been reported by the participating members present no potential for an appearance of a conflict of interest at this meeting when evaluated against the scheduled agenda. However, in the event that the discussions should somehow involve these firms, all participants are aware of the need to exclude themselves from such participation, and their exclusion will be noted in the record. Thank you.

DR. SCHROETER: At this time, we are open for public hearing. We have three individuals who have requested time to make a presentation. The first of these is Dr. Adriane Berman, representing the National Women's Health Network. Dr. Berman?

COMMENTS BY ADRIANE FUGH-BERMAN, M.D.

DR. FUGH-BERMAN: Hello. My name is Adrian Fugh-Berman, with National Women's Health Network. Thank you for this opportunity to address both Committees.

Accutane is unarguably a highly teratogenic drug, affecting one out of four exposed pregnancies. It is also the most effective treatment for severe cystic acne. This is not your run-of-the-mill adolescent pimple outbreak but a persistent, severe, scarring condition which results from tender, acute, localized collections of pus deep in the

DR. WOODLEY: David Woodley, Palo Alto, California.

DR. TSCHEN: Jaime Tschen, Houston, Texas.

DR. STEIN: David Stein, Buffalo, New York.

DR. POMERANZ: Jerome Pomeranz, Cleveland, Ohio.

DR. FLEISS: Joseph Fleiss, New York City.

DR. ABEL: Elizabeth Abel, Stanford, California.

DR. SCHROETER: Arnold Schroeter, Wright State University, Dayton, Ohio.

DR. LUMPKIN: Thank you very much. I now turn the conduct of the meeting over to Dr. Schroeter.

DR. SCHROETER: Thank you, Dr. Lumpkin. I have one statement to make. As I review this decision on tretinoin emollient cream (NDA 19-963), and although it is a dermatologic question and consideration, I believe that there are certain epidemiologic considerations that should be undertaken. I invite the group from Fertility and Maternal Health Drugs Advisory Committee to participate in that discussion whenever they feel that it is pertinent to the ongoing discussion.

At this time, I would like Dr. Isaac Roubein to introduce the group.

DR. ROUBEIN: I have an announcement to make concerning the conflict of interest. Based on the information provided by the participants, the Agency has taken the following actions to preclude any appearances of a conflict

dermis which can break down adjacent tissue, enlarge and form lakes of pus, sinuses and scar tissue.

Most of us can recall the humiliation of ill-timed adolescent pimples. An outbreak always seemed to precede a big date. Cystic acne, however, is on a whole different plane. Long-lasting and disfiguring, the condition may be accompanied by depression, a common companion of highly visible dermatologic conditions. Even after resolution of the acute lesions, deep, ice-pick-type scars remain.

The National Women's Health Network believes that Accutane is a strong, effective, expensive and overused drug. Leaving aside for the moment the serious issue of fetal malformations, Accutane can cause pseudotumor cerebri, hepatitis, corneal opacities, other visual problems, hyperostosis, inflammatory bowel disease and a host of minor side effects. About 25 percent of patients receiving Accutane experience an elevation in plasma triglycerides, which may predispose patients to cardiovascular disease and pancreatitis.

A course of treatment, which lasts 15-20 weeks, for a 60 kg woman will cost between $300-1200. The course may be repeated after an 8-week break, resulting in an expenditure of $2400 for medication alone. This does not include the costs of testing for blood lipid changes, liver function testing and office visits.

Besides its expense, Accutane is not a benign drug and should be restricted to the most severe cases of cystic acne. The number of cases of cystic acne in this country bears little relation to the number of prescriptions written for Accutane. Apparently, the drug is being prescribed for acne vulgaris, the common, milder form of acne which responds to more benign drugs, such as retinoin or benzoyl peroxide. Using Accutane in acne vulgaris is like using an Uzi to shoot a butterfly.

Some cases of cystic acne also respond adequately to standard therapies. Accutane is a potent drug with potentially serious side effects and its use should be limited in both men and women.

None of us is an advocate for birth defects and, as a rule, women do not deliberately try to deform their fetuses. But measures such as monthly pregnancy tests or mandatory hormonal contraception are absurd intrusions. We need to educate doctors to break out the Accutane only on rare occasions. We do not need to subject patients to expensive serum pregnancy tests or a form of birth control that they would not otherwise use.

A female patient using Accutane should be thoroughly counselled on the potential for fetal malformation. The patient must be apprised of risks, that is, the principle of informed consent. But the duty of the physician is to warn.

it is not the duty of the physician to police the patient. It is not the duty of the physician to enforce compliance. The duty of the physician is to warn.

It is offensive to women to assume that we are so untrustworthy and uncaring that monthly blood tests must be performed regardless of whether a woman is abstinent, gay or using contraception. Besides, pregnancy tests do not prevent pregnancy any more than mammograms prevent breast cancer. Early detection is not the same thing as prevention.

While in many situations early diagnostic information is helpful, what exactly is the doctor who required this pregnancy test supposed to do when he catches a woman with a positive pregnancy test? Slap her around? Force her to have an abortion? The doctor can cut off further supplies of the drug but the conceptus has already been exposed in the first trimester to a drug which is teratogenic "in any amount even for short periods", and, at least while abortion is still legal in this country, it is still a woman's choice whether to continue or terminate a pregnancy.

What is accomplished by a monthly pregnancy test besides the erosion of what should be a trusting relationship between doctor and patient and the separation of the patient from upwards of $45 that a serum beta-HCG test costs?

The suggestion that women on Accutane be required to use hormonal contraception is based on strange logic. A

properly used barrier contraceptive can be more effective than an improperly used oral contraceptive, for example. Also pregnancies on hormonal contraception can, and do, occur and hormones are known teratogens.

We live in an era in which court-ordered hearings result in women having C-sections against their will. If the FDA goes along with mandatory pregnancy testing or mandatory hormonal contraception, or an outright ban on Accutane, it will be supporting a dangerous trend, that of viewing a woman merely as a support system for a fetus, even a pre-conceived fetus.

Are we, as physicians, to view all women of reproductive age as incubators to be kept ready for occupancy at all times? What comes next? Most drugs for epilepsy are teratogenic. Are we going to deny these drugs to reproductive-age women? A number of antihypertensive, psychotropic and other drugs are teratogenic. Are we to require hormonal contraception for all these women?

Perhaps eventually we will require monthly pregnancy tests for all women so that we can institutionalize them, force-feed them nutritious food and keep them away from drugs and alcohol.

I am exaggerating (I hope) but I am trying to point out that it is absurd to work from the supposition that we can view women as wombs first and patients second.

The effectiveness of Accutane makes it tempting to use it first without exhausting more benign therapies. We need to reach the doctors who are over-prescribing this drug. It is a useful therapy in limited cases. What we object to is the recommendation that all women using this drug be subjected to monthly pregnancy tests or be forced to take hormonal contraception as the price of obtaining this drug.

DR. SCHROETER: Thank you, Dr. Berman. Next on the agenda in the open session is Miss Alice Guttler, from New Jersey. Miss Guttler?

COMMENTS BY ALICE GUTTLER

MS. GUTTLER: I appreciate the opportunity that you have given me to speak here today. I wanted to come forward because several years ago I began to read articles about the possibility of Accutane either being banned from the market or severely limited to a particular patient population.

I wish I had photographs for you to show "before" and "after" my own personal treatment with Accutane. But I must tell you that it had a profound effect upon my life personally. I suffered from cystic acne for a period of well over ten years. My dermatologist used every form of conventional treatment, including oral antibiotics, the traditional topical creams -- all to no effect, other than the usual side effects, which I am sure the Committee is aware of.

Cystic acne and, indeed, acne vulgaris is a severe

and very debilitating disease. Not only can it have physically devastating effects but it can have severely devastating psychological effects. In my own situation, I refrained from socializing on many occasions; I refrained from going out of the house many times. After my Accutane treatment, however, it truly had a profound effect on the manner in which I carried out my day-to-day activities.

It can be extremely depressing to an individual to have a very poor physical appearance. It can have psychologically devastating effects when you have to go out and function in the marketplace in whatever profession you have or in your social activities.

As I mentioned, in 1982, Accutane was prescribed for me and, quite frankly, I do not know where I would be today had that not taken place. I am, and I was, a woman of childbearing age at the time. My physician thoroughly discussed with me the implications of taking Accutane and, yet, it boiled down to my sense of responsibility as to whether or not I would either be abstinent or take some form of birth control. But I clearly went into that period of taking Accutane with my eyes wide open.

The packaging at the time was different from what it is today and, yet, it contained the clear notice to me that I should not become pregnant during that period of time and I knew full-well what the effect could be but, quite

frankly, the risks did not outweigh the benefits to me because the benefits were, as I mentioned before, quite profound.

I wanted to speak today because I am disturbed by the prospect that those who would disregard the warnings can now perhaps bring about a ban of a particular medication or even a limitation as to who that medication can be prescribed to.

As I mentioned before, to me, Accutane was essentially a cure for a very devastating disease. After I completed my Accutane treatment, it was really a change in my own life style. I went to law school. I became an attorney. I practice litigation. I am out in the public. I have an entirely different perspective on life.

Perhaps I am coming across as somewhat disingenuous, corny or something, but I truly must say to you that before my series of treatment with Accutane, it was quite a humiliating experience not to be able to face members of the public. As I mentioned before, I am an attorney and I am aware of the risk and benefit analyses that an administrative agency like yours must go through to determine the appropriate patient market.

I must say to you that in a case like this, the benefits far outweigh the risks. This is not a case of a failure to warn of a known side effect. Those individuals

who are prescribed Accutane know full-well what they are getting into. It really boils down to a sense of personal and individual responsibility whether they are going to function in an appropriate manner during and immediately after their course of Accutane treatment.

I am, indeed, troubled by how far you have been asked to go to ostensibly protect the public. While the birth of a child with congenital defects is truly a tragedy, the real issue is who is accountable, given that this is a known side effect. For the sake of the many who could benefit from Accutane, I would entreat you not to either ban a medication or to limit it from those in the patient population, such as myself, of childbearing age.

I would also entreat you not to place such onerous burdens upon the taking of the medication that it would dissuade those who could truly benefit from it. Thank you.

DR. SCHROETER: Thank you, Miss Guttler. Our next participant in the open session is Miss Betsy Harkaway. Miss Harkaway?

COMMENTS BY BETSY HARKAWAY

MS. HARKAWAY: Accutane changed my life. I am 26 years old and I was given Accutane in 1983. So I was one of the first people to be prescribed this drug. It took me a long time to find a treatment that actually did something and was very effective and changed my whole outlook on myself,

which at that age, 15-19 -- I do not know if any of you have gone through severe acne or had any acne but you look in the mirror and you see a pimple, and you see the persistence of that pimple, and you do not want to go outside. You do not want anybody to see you. You sit inside. Your whole life and the way you are looking at yourself is changed.

Having Accutane prescribed to me for five months -- my doctor sat me down and told me that I cannot be pregnant while on this drug. I cannot get pregnant. I could and would endure certain side effects of very dry skin, dry mouth, nausea maybe.

When I read articles about people wanting to take Accutane off the market because some people cannot follow directions from the physician and from Hoffmann-La Roche, which has taken measures to ensure patients that this is what you have to go through in order to take this drug -- if you are not going to be responsible enough to follow our instructions, then you should not have this drug prescribed to you.

But I do not think the drug should be taken off the market because a few individuals cannot follow directions that are given to them from their physicians and from Hoffmann-La Roche. I do not think that teenagers should not have an option, if they need to, to use this drug in order for them to have a better outlook on themselves and then on life so that they can carry on and can be normal, functioning people

in society.

I hope that today you will look at that side, that normal people out there are not going outside and are staying in because they cannot look at themselves in the mirror and want people to look at them. I think this drug was very beneficial to me in five months of treatment. I had no problem with acne after that. I think the benefits of the drug far outweigh. Thank you.

DR. SCHROETER: Thank you, Miss Harkaway. We will now move into the open Committee discussion and move to the tretinoin emollient cream discussion. We will have opening remarks by Dr. Carnot Evans. Carnot?

INTRODUCTORY REMARKS, C. CARNOT EVANS, JR., M.D.

DR. EVANS: I would like to welcome all of you here today. I would particularly like to indicate our delight that we have the Fertility and Maternal Health Drugs Committee join our Dermatologic Drugs Committee in the review of these very important items.

The first on our agenda is tretinoin emollient cream, which is a product which has been extensively studied for its effect in the treatment of photo-aged or wrinkled skin.

The application for this product is currently under review by the FDA staff and there was agreement that this was an appropriate time to pose some questions to the Committee

about the drug.

The R.W. Johnson Pharmaceutical Research Institute supplied us with extensive background material and you have additional information supplied to you by the Agency.

The active ingredient in tretinoin emollient cream is tretinoin, a retinoic acid, the acid form of vitamin A. Retinoic acid was first approved for marketing in 1971, under the name of Retin-A cream, for the treatment of acne vulgaris. It has proved to be a highly effective product, especially in comedo acne. Currently, Retin-A is marketed in cream, gel and liquid formulations and in concentrations from 0.25 to 0.1 percent.

Since the publishing of the first article a few years ago, which reported the benefits of Retin-A on photo-aged skin, there has been a surge in the interest of tretinoin-containing products. Sales have increased and there has been a marked rise in media attention.

Firms, other than the R.W. Johnson Pharmaceutical Research Institute, are now testing topical retinoids and there have been several ANDAs (abbreviated new drug applications) submitted for the purpose of demonstrating bioequivalence to the Retin-A products.

In the efficacy evaluation of tretinoin emollient cream, the endpoints are the improvement of the condition of the skin, as observed by the investigator and the patient,

and the conversion to a more normal histological picture. Skin surface replica analyses have also been performed. Is this a useful and reliable measuring tool? If so, how does it compare with the other parameters?

We hope that we can stimulate some discussion today about the margin of safety that can be anticipated with regular application of tretinoin emollient cream to extensive skin areas of pregnant patients over prolonged periods.

We are unaware of any positive demonstration of embryo toxicity with Retin-A use over a 20-year period. Nevertheless, all of these analogs of vitamin A are teratogenic in animals. Tretinoin has been reported by France to be absorbed through normal and dermatitic human skin at 5.2 and 7.1 percent of the dose applied respectively.

Since the no-effect level is unknown, is it possible that the product under consideration could be hazardous in the pregnant state? A recent report by Lammer indicates that the oral intake of 13-cis-retinoic acid during pregnancy has resulted in a high placental and embryonic concentration of tretinoin, which has been known in years "to be extremely teratogenic in all species investigated".

Simply put, is it possible that this product used daily over extensive skin areas could cause embryo toxicity? If it is possible, how great is that likelihood and how should the drug be handled?

We are pleased to have the opportunity to share these background data with you and we look forward to your discussion on this important and timely issue. Thank you.

DR. SCHROETER: Thank you, Dr. Evans. We will now open the discussion on the part of the R.W. Johnson Company. The opening remarks will be by George Ohye, senior vice president.

INTRODUCTORY COMMENTS BY GEORGE H. OHYE

MR. OHYE: Dr. Peck, Dr. Bilstad, Dr. Lumpkin, Dr. Schroeter, Dr. Evans, members of the Committee, ladies and gentlemen, good morning. I am George Ohye, senior vice president of the R.W. Johnson Pharmaceutical Research Institute.

It is my pleasure this morning to introduce Dr. George Thorne, director, clinical research dermatology. Dr. Thorne directed our photo-aging program from its inception, in 1985, and he will chair and moderate our portion of the session this morning. Dr. Thorne?

PRESENTATION BY GEORGE THORNE, M.D.

(Slide)

DR. THORNE: Thank you, Mr. Ohye. We appreciate the opportunity to discuss with the Panel again Renuva, tretinoin emollient cream, shown by extensive clinical testing to be safe and effective for the treatment of photodamaged skin.

(Slide)

The FDA has provided the Panel two questions to consider. The first deals with efficacy determinations. Our presentation will focus on the key efficacy parameters based on investigator and patient evaluations. While we obtained biopsy and skin surface replicas, these are regarded as additional measurements.

The second question involves the effects of prolonged use on percutaneous absorption of topical tretinoin. Today we will present data which show that only minimal absorption occurs even after prolonged use.

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The agenda of our presentation will include a discussion of skin aging, protocol development and a brief description of the clinical methodology used in the studies with Renuva.

Dr. Schwab will describe the conservative and focused statistical method used to analyze our data. Dr. Worobec will then present the results which largely validate our experimental design and the adequacy of our efficacy parameters.

(Slide)

Dr. Wills' presentation will provide data from recent percutaneous absorption studies that indicate that tretinoin is minimally absorbed through photodamaged skin. I

will summarize the discussion from the last Advisory Panel meeting when they agreed that topical tretinoin did not pose a teratogenic problem. After this summary and conclusions we will answer questions.

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In addition to the speakers, we have several scientists from our Company, Dr. Powers, from toxicology; Dr. Ng, from formulations; and Dr. Mezick, from pharmacology.

(Slide)

Additionally, we have invited Dr. Gary Grove, whose group analyzed the skin surface replicas, and Dr. Tom Nigra, a clinical investigator in the Renuva trials.

As you can see, we have a full agenda. So if you could hold your questions until the end, we can complete our presentation in the time allotted.

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The subject of this NDA is Renuva, 0.05 percent tretinoin, in a specially designed base which provides a high degree of emolliency for patients with photodamage. Renuva is a water and oil emulsion, in contrast to Retin-A cream which is indicated for acne and has an oil and water formulation.

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The proposed indication for Renuva is the treatment of photodamaged skin. Patient benefits include reduction of

fine wrinkling; mottled hyperpigmentation and roughness. Proof of efficacy for this indication are the results from the extensive clinical studies using Renuva.

(Slide)

Let's review the role of photodamage in skin aging. Visible signs of aging can be due to a number of causes but the passage of time and the exposure to the environment are the most important. For protected skin chronologic aging is most evident, while on exposed surfaces photodamage causes most of the visible signs of aging.

(Slide)

Clinical features of chronologic aging are due to thinning of the epidermis and the dermis. This condition is not reversible. The body cannot repair chronologically aged skin.

(Slide)

Photodamage is a term used by dermatologists to define a skin disease caused by chronic sun exposure. Most important, and in contrast to chronologic aging, photodamage is reversible. Photodamage can be thought of as a wound caused by chronic minor trauma. By avoiding or reducing the injury, in this case sun exposure, in time the body can heal the damage.

(Slide)

Photodamage progresses through several stages,

beginning as early as the teen years and, in many cases, eventuating into skin cancer. Specific clinical and structural features of photodamage have been well described.

Let's focus our attention on the middle stage. This group has photodamage with little chronologic aging and has a low incidence of visible actinic keratoses and skin cancers. These generally occur in the later stages. Thus, they provide a good study population for photodamage. Since photodamage does progress into skin cancer, it is obvious that we need to interrupt the progression of this disease.

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Prevention is the cornerstone in the management of photodamage. The public must be educated to avoid the harmful rays of the sun, apply sunscreens and wear protective clothing.

(Slide)

Other therapeutic modalities include emollients which may smooth rough skin and counselling on proper skin care, such as avoiding irritants and overexposure to the sun. Additionally, the routine use of sunscreens may help repair the skin by preventing the continual damage caused by everyday sun exposure.

As a reminder, all patients in the study using Renuva applied moisturizers and sunscreens. Additionally, they received monthly counselling by dermatologists on proper

skin care.

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It is noteworthy that older acne patients using topical tretinoin were the first to report that their skin looked and felt better. An important clue to the action of topical tretinoin came from studies using photodamaged mice. The studies showed that tretinoin accelerated the healing process by laying down new collagen in the subepidermal repair zone. Also in uncontrolled studies beneficial responses were seen in patients with photodamaged skin.

(Slide)

The excitement about a potential topical treatment for photodamage stimulated us to design protocols and to develop efficacy parameters.

(Slide)

We began this model development with three pilot studies using Retin-A cream. The pilot studies have all been published and are included in your material. I do want to emphasize the methods as they provide valuable information for future conduct of photodamage studies.

First, all were double-blind. Two were parallel groups for the face and paired comparison of the forearms. One was a paired comparison for both the face and the forearms.

The lowest concentration of Retin-A cream tested

was 0.05 percent. The studies were all vehicle controlled, lasting up to 6 months. One study evaluated middle stage photodamaged patients, similar to our studies using Renuva.

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The individual clinical signs selected for study encompass those from classical descriptions of photodamaged skin by Kligman, Marks and others. The evaluation scales included the visual analog type, which was later modified for use in studies with Renuva. Biopsies and skin surface replicas were performed which provided additional information.

(Slide)

Based on the significant results of these pilot studies, we had several meetings with the FDA to discuss protocol design and analysis plans. Since this was a new therapeutic class, no FDA guidelines existed. In 1987, we presented data from the pilot studies to the FDA Advisory Panel. In the fall of 1988, we met again to discuss the clinical program. Later in the fall, we outlined our statistical analysis plan.

(Slide)

Helpful suggestions from the FDA, Advisory Panel, consultants and investigators were incorporated into the studies using Renuva. We chose parallel group design for our facial studies because of the possibility of translocation of the test creams.

The question about controls is more difficult. We believe the best control, in addition to the vehicle, would be lower concentrations of tretinoin. We were asking the question whether investigators and patients could detect an efficacy difference between Renuva and its vehicle during simultaneous testing of other concentrations of topical tretinoin.

Patients with mild to moderate photodamage were chosen because they had a low incidence of visible actinic keratoses, skin cancers and less chronologic aging. Study length of six months was selected to allow adequate time for therapeutic results.

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Following the suggestions of the FDA, we focused our attention on three key efficacy parameters, based primarily on investigator and patient assessment. Other measurements were supportive, such as ratings of individual clinical signs by the investigator and skin features by the patient.

(Slide)

Now let's turn our attention to the protocols using Renuva. Three studies, two multi-center and one single investigator study, have been filed to this NDA.

In the first study, in addition to Renuva, the vehicle and two other concentrations were investigated; in

the second, one other. The third study was similar to our early pilot studies. In this study, in addition to the face, forearms were also evaluated in a paired-comparison manner.

(Slide)

All patients were required to have mild to moderate photodamage and be between the ages of 30-50. No visible actinic keratoses should be present, nor history of skin cancer.

(Slide)

This slide illustrates the study events. The key efficacy parameters are highlighted in yellow. The global evaluation was done by the investigator at week 24; overall severity at each visit; and the patient's overall self-assessment at week 24.

Color photographs were taken at baseline, 3 months and 6 months as a reference for the investigator to help him in grading the patient's response. Examples are available, if you would like to see them after the presentation, during the question and answer session.

At baseline and 6 months 2 mm punch biopsies were taken. Skin surface replicas were obtained at baseline, 3 months and 6 months.

(Slide)

This slide illustrates how the investigator reported his global evaluation. This was done at the end of

therapy but was compared to baseline.

(Slide)

The investigator made a determination of overall severity on a 10-point scale at each visit. At entry, all patients had a rating between 6-1.

(Slide)

The patient's assessment was based on their answer to the question, overall, compared to when I began using the treatment my skin is worse, the same, somewhat improved or much improved.

(Slide)

All 8 individual clinical signs of photodamage were measured for the entire face at each visit. These measurements formed, in part, the composite overall severity score. Definitions of the clinical signs have been provided in your material.

(Slide)

Like the investigator, the patient reported an evaluation of their individual skin features.

(Slide)

Other measurements included skin surface replicas and skin biopsies.

(Slide)

Skin surface replica evaluation has been published by Dr. Grove and is in your material. So, in the interest of

time, I will just summarize the technique. Silflo, a dental impression material, is mixed with a catalyst --

(Slide)

-- and placed in electrode rings in the crows feet area and the cheek. There it polymerizes and becomes a permanent record of the skin topography.

(Slide)

This is an example of a skin surface replica, showing the fine detail of the topography of photodamaged skin.

(Slide)

The 2 mm punch biopsies were sent to Boston University Department of Dermatology for processing into both plastic and paraffin sections. The 7 microscopic features that were measured for the epidermis are listed here.

(Slide)

Additionally, 4 dermal parameters were evaluated.

(Slide)

Microscopic features, listed on this slide, were graded directly by light microscopic observation.

(Slide)

This is an example of a slide from a plastic-embedded section, stained with toluidine blue, showing excellent morphologic detail which allowed the pathologist to accurately grade the effects of topical tretinoin on the

skin.

(Slide)

Four parameters were evaluated using innovative image analysis techniques.

(Slide)

Here is an example showing computer-enhanced image analysis measurement of the epidermal area and the area of the papillary dermis.

(Slide)

Let me again emphasize the key efficacy parameters: Investigator's global evaluation at the end of therapy; overall severity rating of photodamage measured at each visit by the investigator; and the patient's overall self-assessment done at the last visit.

(Slide)

Other measurements included individual signs rated by the investigator and individual skin features rated by the patient. These ratings help to characterize the time response and the benefit patients will derive from treatment with Renuva.

Skin replicas were shown in a pilot study to be a useful adjunct in measuring the response of the skin surface to topical tretinoin therapy. This response appeared to be related to improvement in roughness and wrinkles. Skin biopsies were intended to define the mechanism of action and

investigate the microscopic structural changes following prolonged use of tretinoin.

(Slide)

Now I would like to introduce Dr. Barry Schwab, who will present the statistical overview of the studies using Renuva.

PRESENTATION BY B. SCHWAB, Ph.D.

DR. SCHWAB: Thank you. Today I will be discussing the statistical aspects of the tretinoin emollient cream studies for photodamage. The details of what I will be discussing are contained in the written document that has been provided to the Committee members. What I would like to do is just briefly go over the approach to the data analysis that was taken as a preface to the presentation of the results by Dr. Worobec.

(Slide)

Essentially, I will be covering four points today in my talk. The first one deals with our a priori determination of the key efficacy parameters of the study and the importance of this from a statistical point of view; secondly, adjustments to significance levels that were made in accordance with the multi-center trials. The third point has to do with additional intent-to-treat analyses that were conducted and, finally, our evaluation of the consistency of results across centers.

(Slide)

The first point deals with our focus on three key efficacy parameters. Prior to the establishment of our data bases and prior to the statistical analysis, a meeting was held between representatives of the Robert Wood Johnson Pharmaceutical Research Institute and FDA's Division of Biometrics. At this meeting, our analysis plan was discussed and our specification of three parameters as being the primary parameters of the study was presented.

(Slide)

Again, these three parameters are the investigator's global evaluation at the end of therapy; the overall severity of photodamage, which was rated on a 10-point scale at baseline and at each subsequent visit; and, thirdly, the patient's overall self-assessment from the end of therapy questionnaire.

Importantly, this a priori designation provides for focused statistical inference and guards against searching through the data for significant findings.

(Slide)

Another approach that was taken is that appropriate adjustment to the statistical significance levels was made in accordance with the design of the multi-center trials.

(Slide)

A feature of the multi-center studies is that

various concentrations of tretinoin emollient cream were included. For example, in multi-center study 1, 3 concentrations of tretinoin emollient cream are included, as well as a vehicle cream treatment group. So based upon this design, appropriate methodology to account for these 3 comparisons was employed.

The procedure that was used is referred to as the sequentially rejective Bonferroni procedure and I would like to just briefly illustrate the stringency imposed by this technique.

First, the p values for each comparison of tretinoin versus vehicle would be computed and ordered from smallest to largest. Then, rather than testing each at the 0.05 level of significance, the first comparison would be declared statistically significant only if the p value is less than 0.017. If it is, testing continues and the second comparison is compared to the 0.025 level and, finally, the third p value, corresponding to the third comparison, would be tested at the 0.05 level.

This approach is appropriate for the design at hand but, importantly, gives the desired level of protection against declaring differences between treatment groups when, in fact, no difference exists.

(Slide)

The next point I would like to make has to do with

additional intent-to-treat analyses that were conducted or analyses including all patients enrolled into the trial.

For our primary analyses, subjects may have been excluded due to non-compliance or insufficient time on therapy. Overall, the validity rates were quite high, however. Approximately 93 percent of the subjects in the first multi-center trial were included in the statistical analysis and approximately 85 percent of the subjects in the second multi-center trial and the single-center trial were included in the analyses.

However, for completeness, additional intent-to-treat analyses were conducted in multi-center trial 2 and in all cases the results were in agreement with the conclusions drawn from the primary validation analyses. Just as a note, the results that Dr. Worobec will be presenting are based on the valid patient analyses.

(Slide)

Additionally, the consistency of results across investigators was evaluated via the statistical model. The results of our analyses indicated generally no significant trend by investigator interactions, signifying the consistency of treatment differences from one investigational site to the next within the multi-center trial. Observationally, we also noted consistent findings from one study to the next.

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So to summarize, a conservative approach to the data analysis was taken, one that accurately reflects the design and intent of these clinical trials. Based on this approach, we observed consistent, reproducible results both within the multi-center trials, as well as across the three studies.

(Slide)

I will now introduce Dr. Worobec, who will present the efficacy and safety results from the clinical studies.

PRESENTATION BY S. WOROBEC, M.D.

DR. WOROBEC: Thank you. Members of the Committee, ladies and gentlemen, I will now present the results of the clinical studies.

(Slide)

These studies were conducted by nine investigators in geographically diverse areas of the United States.

(Slide)

In the first study 320 patients were enrolled and 93 percent completed the study. In the second multi-center study 299 were enrolled and 88 percent completed the study. In the third study, the design of which followed that of the pilot study, 40 patients were enrolled and 85 percent completed the study.

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The patient characteristics were that the age

ranged from 29-58 years; 19 percent were men and 81 percent were women. The grading of the overall severity of photo-damage was mild for 35 percent; moderate for 65 percent. A single patient, with an overall severity grading of 7 placing her in the severe category, was also enrolled.

(Slide)

The efficacy parameters, which were presented by Dr. Thorne, were as follows: The key efficacy parameters; individual clinical signs and patient self-assessments; and measures of the skin structure and surface.

(Slide)

We will first go over the results for the key efficacy parameters, that is, the global evaluation, the overall severity of photodamage at the end of the study compared to baseline and the overall patient self-assessment.

(Slide)

In this and the following slides the bars represent the percent of patients improved. There is one set of bars for each study. The first multi-center study is on the left. The second multi-center study is in the middle and the third study is on the left.

Please focus on the green column which represents patients treated with Renuva or tretinoin emollient cream 0.05 percent, and the blue column which represents vehicle-treated patients. The asterisks in this slide and all the

ones that follow indicate that a statistically significant result was present between the Renuva and vehicle-treated groups.

In this slide we see the results for the first key efficacy parameter, that is, the global evaluation of improvement at the end of the study compared to baseline. A greater percentage of patients improved in the groups treated with tretinoin emollient cream 0.05 percent than the vehicle treatment groups.

In the third study there were 18 patients in the tretinoin emollient cream 0.05 percent group and 16 in the vehicle group. Therefore, despite the difference seen here, statistical significance was not achieved.

(Slide)

The second key efficacy parameter was the investigator's rating of improvement from baseline in the overall severity of photodamage. A greater percentage of patients showed improvement in the tretinoin emollient cream 0.05 percent group than the vehicle treatment group. This difference was statistically significant in all 3 studies.

(Slide)

Here is the third key efficacy parameter, the overall patient self-assessment at the end of the study. More patients applying Renuva, tretinoin emollient cream 0.05 percent, rated themselves improved than those who were

treated with the vehicle. This change was statistically significant in the second large multi-center study.

(Slide)

Now let's look at the individual clinical signs. First we will look at the improvement as rated by the investigators. Then we will see the patient self-assessments.

Three of these, fine wrinkling, mottled hyper-pigmentation and roughness, are designated in yellow, meaning that these were statistically significantly improved in both large multi-center studies. Laxity was significantly improved in one multi-center study.

(Slide)

Here are the individual features as rated by the patients. More patients treated with Renuva 0.05 percent rated themselves improved than those treated with the vehicle. Improvement in all of these was statistically significant in the second multi-center study and improvement in some was significant in more than one study group.

(Slide)

Now we see the consistency of the evaluation of improvement in three individual clinical signs, which are presented here for fine wrinkling, mottled hyperpigmentation and roughness, as rated by the investigators and patients.

(Slide)

We will now go on to the measures of the skin

surface and structure that were done.

(Slide)

The skin surface replicas were analyzed by a central investigator, May Joe Grove. Upon receipt, each replica was placed upon a turntable stage, seen by her hand. A light was shined upon the replica along the lines of the major skin creases. This was termed the east-west orientation. Then measurements were taken in a perpendicular direction, termed the north-south orientation. A video image, (upper right) was captured by a computer and analyzed. A mathematical curve (lower right) was generated for the light and dark areas. This led to the derivation of R_a and R_z values which are explained in the following slide.

(Slide)

The R_z value is the average distance between the tallest peak and the deepest valley within each of five segments across the replica. Ten such scans were performed for each replica. The R_a value is the average of the areas within the peaks and valleys, created when a central line is drawn across this curve. Both values measure surface features, such as roughness and wrinkles.

(Slide)

Shown here is an example of the changes seen of the results of a single value, the crow's foot R_z value in the east-west orientation from the first multi-center study.

What we see here is the percent change from baseline for each treatment group. A zero value means no change from baseline to the end of the study at week 24. A positive value means that this R_z value increased and a negative value means that it decreased or that a flattening of the surface had occurred.

(Slide)

Here are the results for values analyzed within the second multi-center study, showing the decreases seen at 6 months of tretinoin emollient cream 0.05 percent treatment versus vehicle treatment. Complete tables for all the studies are presented in the booklet which you have received for this meeting.

(Slide)

Now let's look at the skin biopsy results at the studies' end compared to baseline. The data from the first two large multi-center studies will be presented and data from the third study are currently being submitted.

The parameters shown here in yellow represent those for whom there were statistically significant changes present in both multi-center studies. Melanin content decreased to a statistically significant degree in one study. There are no changes from baseline in the other histologic parameters, which were studied directly by light microscopy or by image analysis.

(Slide)

Epidermal thickness increased by an average of 33 percent in both multi-center studies for patients treated with tretinoin emollient cream 0.05 percent.

(Slide)

Here is an example of the increased epidermal thickness in one biopsy. The baseline biopsy is shown to your left and the end of treatment biopsy is shown to your right.

(Slide)

Next are the changes detected in the granular cell layer thickness. The granular cell layer increased by an average of 55 percent consistently in both multi-center studies.

(Slide)

Shown here is an example of a baseline biopsy (on the left) where the granular cell layer is 2 cell layers thick; and a 24-week biopsy from the same patient (on the right) in which the granular cell layer is 4-5 cell layers thick on a teluidin blue stained section.

(Slide)

The stratum corneum changed from a woven to a compact morphology in approximately 70 percent of patients treated with tretinoin emollient cream 0.05 percent in both multi-center studies.

(Slide)

This slide illustrates the change from a baseline woven stratum corneum (on the left) to a compact stratum corneum at 24 weeks (on the right).

(Slide)

These measurements of the change in skin structure are in the same direction as the key evaluations of tretinoin emollient cream 0.05 percent efficacy in the treatment of photodamage.

(Slide)

Now let's review the safety parameters for all the studies combined. These consisted of the direct elicitation of the signs and symptoms of skin irritation at each visit, and a collection of adverse event data at each visit.

(Slide)

The signs and symptoms of skin irritation were rated on a 10-point scale at each visit.

(Slide)

The height or the retinoid response occurs at week 2. Here we see the mean grades for individual parameters at week 2 and they are greater for the tretinoin emollient cream 0.05 percent group than for the vehicle group. However, they are mild for the vast majority of patients. So the mean grade is within the mild category for each of these parameters. These signs, while persisting, gradually decreased during the course of the study.

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Further safety data were collected during 3 extension studies. In the second one, all patients either discontinued or decreased their application to once or three times a week. In the third extension study, 435 patients were entered, of whom 360 completed the study. So for this group we have up to 2.5 years safety data.

(Slide)

The non-cutaneous, systemic adverse events occurred in a low incidence and those which were reported for the tretinoin emollient cream treatment group were comparable to those reported for the vehicle.

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No systemic retinoid adverse effects have been reported by the investigators.

(Slide)

In summary, we have demonstrated consistency in the results across the key efficacy parameters. The superiority of Renuva 0.05 percent over vehicle is demonstrated by the three key efficacy parameters, two of which were rated by the investigator, that is, the global and the overall severity, and one rated by the patient, their own self-assessment of what their improvement had been.

(Slide)

This superiority is also shown by additional

parameters which include the individual signs of photodamaged skin as rated by the investigator and the patient, biopsy results and skin surface replica analysis.

(Slide)

I will now introduce Dr. Rob Wills, who will speak about the percutaneous absorption studies that have been performed with tretinoin in various formulations. Dr. Wills?

PRESENTATION BY ROB WILLS, Ph.D.

DR. WILLS: Good morning. What I am going to present to you is our data on the percutaneous absorption of tretinoin. I will also place these data into perspective with respect to endogenous circulating concentrations of tretinoin.

(Slide)

With that, I would first like to review what is known about the percutaneous absorption of tretinoin. In the six studies you see before you, radiolabeled tretinoin was applied topically in either healthy subjects, patients with acne or patients with psoriasis.

What you can see in the column labeled "absorption" is that the absorption was minimal and the percent recovered in the urine, for the most part, ranged from less than 1 percent up to approximately 8 percent of the applied dose. In 1 study they also looked at feces. So this is a cumulative amount. However, in none of these studies did they profile

the radioactivity in plasma.

(Slide)

In our studies we wanted to look at the percutaneous absorption of Renuva and compare this to that of Retin-A, a product on which we have a tremendous amount of clinical experience.

We used healthy male subjects. The test article was ^{3}H-tretinoin. We applied a 50 mcg dose of tretinoin to the area of the face. This is the target tissue for safety and efficacy.

(Slide)

We looked at 5 test groups. We applied a single application of radiolabeled drug Renuva to naive patients. We also applied a single radiolabeled application of Renuva after 28 days of daily application of unlabeled drug in the second scenarios. We repeated these 2 scenarios for Retin-A and we have just completed a single application of radio-labeled drug after 1 year of therapy using Retin-A. In all these studies we collected urine and feces for 7 days and plasma up to 72 hours.

(Slide)

Our results were consistent with what has been reported in the literature. Here is the cumulative percent of the applied dose recovered in urine. If you look out in time after collection, the percent recovered ranges from

approximately 0.6-1.8 percent of the dose. There was no difference between formulations in time of therapy, again suggesting minimal absorption.

(Slide)

The same case was true for feces. In this case there was less percent recovered, approximately 0.6 percent of the applied dose. Unfortunately, at the time of this presentation, we have not completed the analysis after 1 year of therapy.

(Slide)

As I mentioned previously, the other studies reported in the literature had not measured or followed plasma radioactivity. We happen to have done that. What you see here is the picogram equivalence of tritium-labeled tretinoin per milliliter of plasma versus time after application.

As is typical with these curves, concentrations rise with absorption and then decline with distribution and elimination. As you also can see, the amount that we are peaking after a single application is in the 20 pg/mL range, again supporting a minimal absorption of these formulations. These profiles appear to be independent of the formulation and time of therapy. In fact, even here there is a trend for diminished absorption after 1 year of therapy.

(Slide)

Where did those small picogram/milliliter levels fall with respect to endogenous concentrations? In these 4 studies which are summarized from the literature, the endogenous concentrations ranged from 1 to about 7 ng/mL. This is approximately 100-fold what we observed from our single applications.

Unfortunately, the best analytical method today will not allow us to profile intact tretinoin or any of its metabolites in that low picogram range. So to get a handle on accumulation we need to project based on the radioactivity curves.

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If we do that and compare that to endogenous concentrations -- as you recall endogenous concentrations are in the 2-6 ng/mL range -- for Retin-A at the recommended dose applied daily, we would predict 0.3 ng/mL steady state concentration. Renuva at our suggested dose would provide a steady state concentration of 0.5 ng/mL, which is 15-40-fold less than is circulating endogenously.

We would also like to state that this level, even though it is projected, is probably an overestimate because it includes, as you know, radioactivity which has tretinoin in its metabolites. But, clearly, these low levels would not contribute significantly to the body pool of endogenous retinoic acid.

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In conclusion, we have demonstrated that the absorption of ^{3}H-tretinoin is minimal from topical application of Renuva and that the additional body burden of tretinoin from realistic topical doses of Renuva is insignificant and would be an unlikely source of systemic toxicity or teratogenicity.

Thank you. With that, I will turn the podium over to Dr. Thorne.

PRESENTATION BY GEORGE THORNE, M.D.

(Slide)

DR. THORNE: Thank you, Dr. Wills. We presented an update of our photodamage studies at our last FDA Advisory Panel, in the spring. At that time, I stressed that the method of application of topical tretinoin for photodamage is comparable to acne treatment. Importantly, topical tretinoin has an excellent safety record of over 18 years, with approximately 16 million patients applying it and very few having reported an adverse reaction. The vast majority of those adverse reactions were limited to local effects.

In addition, I presented data addressing the minimal percutaneous absorption, which makes the possibility of systemic toxicity from topical tretinoin remote.

Dr. Rosa discussed the results of two FDA epidemiological studies which suggested that any relationship

between topical tretinoin and fetal abnormalities was consistent with chance occurrence.

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After review of the written and oral material, the Panel voted unanimously that topical tretinoin did not now pose a teratogenic problem.

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In summary, Renuva, with its high emolliency formula, has been specifically designed for the treatment of photodamage. Photodamage can be a serious skin disease, characterized by specific visible signs which include fine wrinkling, mottled hyperpigmentation and roughness. In addition, microscopic damage occurs to the epidermis which might eventuate into skin cancer.

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Pilot studies suggested that clinical parameters could be used to demonstrate efficacy. The FDA, the Advisory Panel, consultants and investigators all provided valuable input into the protocol design.

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The first question for the Panel dealt with the efficacy parameters. During our presentation, we focused on three key parameters involving the investigator and patient evaluation. All of the variables should be considered additional data.

We used a focused, conservative statistical analysis which demonstrated consistent results across the three studies.

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This slide illustrates the consistency of the key efficacy parameters for all patients using Renuva and 78 percent of the patients treated with Renuva had global improvement after 6 months of therapy, compared with 43 percent for the vehicle group. Remember, the vehicle treatment group received the best currently available topical treatment for photodamage.

Of the patients applying Renuva, 68 percent showed improvement in overall severity, compared with only 38 percent for the vehicle.

Lastly, 81 percent of patients -- the ultimate judges of efficacy for this indication -- believed they improved after using Renuva for 6 months.

(Slide)

The measurement of the effects of Renuva on individual clinical signs provide patients a guide as to what benefits they might have and when they may occur. Fine wrinkling, mottle hyperpigmentation and roughness were most consistently improved during our 6-month studies.

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Renuva produced 3 consistent changes in the

microscopic structure of photodamaged skin: An increase in the area of the epidermis; an increase in the granular layer thickness; and a change in the overall appearance of the stratum corneum.

(Slide)

The results from computerized analysis of skin surface replicas reinforce the investigator and patient observation that fine wrinkles and roughness were improved with Renuva.

(Slide)

Your second question regarding percutaneous absorption of tretinoin after prolonged used was clearly answered by data presented by Dr. Wills. It is obvious that minimal amounts are absorbed even after prolonged use on photodamaged skin.

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Your written material contains these calculations but I would like to highlight the safety factor, which is at least 20,000. This is based primarily on a dose of 250 mg applied to the face, and that is really where we expect Renuva to be used. So at least 20,000-fold safety, based on oral teratogenicity studies in rats, is evident.

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In conclusion, we have presented data based on extensive clinical testing which has shown that Renuva,

applied once daily, is safe and effective for the treatment of photodamaged skin with improvement in fine wrinkling, mottled hyperpigmentation and roughness. Potential risks are limited to local irritation and the potential for any long-term cutaneous or systemic toxicity is remote.

Thank you for your attention and we would be glad to answer questions now.

DR. SCHROETER: Thank you, Dr. Thorne. Dr. Thorne, would you mind staying at the podium to field questions, either for yourself or for your staff?

I will open up the discussion now to both Committees and to address the questions that you may have to R.W. Johnson Company. Yes, Dr. Fleiss?

DR. FLEISS: I have a couple of questions on design and statistics. The investigators seemed to be more sensitive to treatment effects than the patients. Is there a chance that the blinding that they were presumably working under was somehow broken? Were there clues as to which patients were getting active and which were getting just vehicle?

DR. THORNE: One of the interesting things about topical tretinoin therapy is the effects that retinoids have on the skin. What we tried to do in this study was to add enough factors, such as additional concentrations of tretinoin, to help confuse the investigators so that any kind of unblinding would not be a factor. In fact, there was not

really a very good association of factors such as irritation, the peeling and redness that we saw that the retinoids caused with activity. So to answer your question, we do not think that there was any biasing.

DR. FLEISS: On the statistical end, there was a report that the intention-to-treat analysis confirmed the efficacy analysis -- with respect to statistical significance or just with respect to direction of difference?

DR. SCHWAB: Actually, both. They confirmed in every way the conclusions that were drawn. We would see the same statistical significance and again the same directions. Because in the valid patients analysis so few patients were excluded, we saw consistent findings.

DR. FLEISS: One final statistics question, you used this sequential Bonferroni procedure. Why not the Dunnett procedure?

DR. SCHWAB: We felt that this was good. It had nice statistical properties, power properties and it was not very labor-intensive. So it certainly is, we felt, an appropriate procedure to apply.

DR. POMERANZ: I wonder if you would further define local irritation. It is hard for me to believe that none of these patients had any undesired side effects. I wonder if any of them wandered out into the sun, which sometimes aggravates patients.

DR. THORNE: As I mentioned, all patients in the Renuva studies were instructed to avoid excessive sun exposure and to use sunscreens. Actually, the number of any problems associated with the sun are really very minimal.

DR. STEIN: I have some further questions about methodology. Did you look at the reproducibility of your skin surface replica results in a model of some sort in an in vitro situation?

DR. THORNE: The skin surface replica material in our study was, again, additional information. We used it not really to see how they actually directly related to the clinic because the entire face was used for the clinical evaluation. Dr. Grove, who is with us today, did do studies where he actually evaluated the skin surface replica and how that was related to the clinical signs in the areas that the skin surface replicas were done. That material was supplied to you and it has been published. If you would like to have more information, Dr. Grove is available to speak to that point.

DR. STEIN: That is good. I am aware of that. But did you look at the reproducibility of the technology itself? Was there any question about that?

DR. THORNE: No, all the samples were sent to Dr. Grove. They looked at all of them as far as techniques were concerned and over 80, 90 percent of them were evaluable. So

they were evaluable and were of high quality.

DR. STEIN: Okay. So you were satisfied with that. If you were, then why wasn't it weighted more or used more in your overall evaluations?

DR. THORNE: Again, we focused on the two major factors in our studies, the patient and the physician evaluation of the skin. At the time we were doing the studies, we did not have a lot of information about skin surface replicas. While they are helpful, it still depends on what the patient sees and what the physician can evaluate with his hands, just as you would do with a patient who comes into your office.

DR. STEIN: I realize the technique is very new and I guess the point I am trying to make is that I think it has a lot of potential from what I have read about it, what I know about it and from what you presented today.

I am wondering if it could potentially be much more objective. I am a little concerned about the subjectivity of your global evaluations and I am wondering if potentially, especially if we are looking at vehicles and ideal concentrations, that technique might be much more valuable and if you might put greater weight in the future on that. You did show some statistically significant results that were published --

DR. THORNE: Right.

DR. STEIN: -- and I am just wondering if you should emphasize that more in the future.

DR. THORNE: Certainly, the results of our skin surface replicas were consistent with our clinical results and they were statistically significant. I agree that in the future it certainly may be a valuable adjunct to studies of photodamage.

DR. STEIN: I think it would be nice to eliminate some of the subjectivity, which was referred to previously, in your investigator evaluations.

DR. THORNE: Again, the evaluations were all very, very consistent. You would think that there would be a lot of noise in this but really there was not very much. There was very good consistency even with all of the additional concentrations of tretinoin.

DR. TSCHEN: Is it possible that edema and cellular infiltration accounts for some of the thickening in the epidermis and dermis? Was that looked at?

DR. THORNE: As you know, in the pilot studies this was looked at very closely by Dr. Voorhees and others, and really very little edema was seen in any of the biopsies, either clinically or under the microscope. In our studies we did biopsies at baseline and at 6 months and we saw virtually no inflammation and no evidence of any irritation, even after 6 months of therapy. So I think the answer is no.

DR. ABEL: I would like to come back to the issue of the photosensitivity. I was wondering what type of sunscreen was recommended. Was this a specific SPF number? Also how does the acute photosensitivity affect the per-cutaneous absorption? Were the absorption studies done in patients who were using sunscreens regularly? Also could you go into the issue of photodegradation and what happens to the metabolism of Retin-A with photodegradation? This information refers to the 13-cis-isomer.

DR. THORNE: The first question --

DR. ABEL: The sunscreen recommended. Was there a difference in the patient who used sunscreens and those who did not?

DR. THORNE: We provided all of our patients with Sundown. However, they were free to use any sunscreen they wanted and they were all at least SPF-15.

DR. ABEL: The second question is, would there be a difference in the absorption studies in the patients who used sunscreens and did not use sunscreens? Also how was it photodegraded?

DR. THORNE: The studies that Dr. Wills reported on, for 28 days pre-application all the patients were given sunscreens and told to avoid sunlight, just as any other Retin-A patient would be. So those were all done in the face of sunscreen applications, to the best of our knowledge. We

cannot tell because we did not have a control group that did not use sunscreens. So they all used sunscreens.

DR. ABEL: They all used sunscreens?

DR. THORNE: Right.

DR. ABEL: All right. What are the studies on photodegradation and the 13-cis-isomer?

DR. THORNE: We have not done any particular absorption studies looking for 13-cis or photodegradation. You have to understand that the amount that gets through the skin is so infintesmally small that it is very difficult to quantify those sorts of things.

DR. WOODLEY: I wanted to ask you a question about the skin replica stuff again. Your vehicle is an emollient and my mother tells me that when she puts vaseline on here face, her wrinkles get a lot less noticeable. If I read you results correctly, it looks as if the vehicle itself actually make the skin replicas worse. There was a positive number. That would be somewhat against what most women would think, or maybe men too, who are applying emollients to wrinkled skin. They usually feel they look less noticeable. So I am trying to figure out why your vehicle actually had objective results that were a worsening of the wrinkling -- your R_a and R_z values.

DR. THORNE: One thing I did not mention was that all patients were required to stop using their emollients and

the test creams 48 hours before they took the replicas. Also this was done toward the wintertime when the skin tends to be rougher. So I think that is one of the attributes of tretinoin to the emollient. It did not make the skin smoother even after stopping for 48 hours.

DR. WOODLEY: You had a range of patient ages from 29, I think, up to 50 or so. Were there differences in the skin replica R_a and R_z values depending on age? I mean, you would predict that a 29-year old would be different from a 50-year old.

DR. THORNE: Baseline difference?

DR. WOODLEY: Yes, baseline difference because it would give some validity to that procedure.

DR. THORNE: Dr. Schwab, do you recall any statistical differences?

DR. WOODLEY: Specifically in the ages of the 29 versus --

DR. THORNE: You know, there were not that many. The mean age was 43 or so and most everybody clustered around that. So I do not think that we probably had a large enough piece of data from our studies to segregate them.

DR. GROVE: I do not know if you have done it in your studies but we have done other studies where we have looked at the relationship of the R_a and R_z parameters with age, as well as severity of photodamage. The more important

component is the degree of photodamage because you can have individuals who are, say, age 50 who have the same chronological age but have completely different physical appearances, largely due to whether they have had outdoor exposure, occupational -- tennis players, golfers, versus people who had worked inside, used sunscreens and so on. So the more important correlation is towards the degree of photodamage and the replicas do correlate very nicely with that. But also there is a very good correlation with age, but it is the photodamage that is the better correlation.

DR. SCHROETER: You are from R.W. Johnson?

DR. THORNE: No, this is Dr. Gary Grove.

DR. SCHROETER: Please identify yourself. Anybody using the microphone, please identify yourself.

DR. GROVE: Dr. Gary Grove.

DR. SCHROETER: In addition to that question, before I let my other colleagues ask questions, Dr. Thorne, I realize that you have some age-defined parameters here. I see no one in the seventh decade here. The group was not randomly selected?

DR. THORNE: No. We really set out to look at one age group, the people with mild to moderate photodamage, because they really have photodamage with a lot of chronological encumbrances, such as skin cancers and actinic keratoses, which I think should be treated in a different manner. That

is why we did not choose this particular population for these studies.

DR. SCHROETER: Yes, but therein lies a significant factor. If you are going to eliminate those in the seventh decade of life or even the sixth decade of life, you are eliminating a number of people who are going to be using this and are they more difficult to treat? Are you implying that by your choice of a less severe photodamaged patient?

DR. THORNE: No, we set out to specifically look at this patient group because of the other attributes that they lack. We have other studies, for other reasons, with higher concentrations of tretinoin which we think will be more appropriate for patients with actinic keratoses and other sorts of things. But this particular age group that we are looking at in the studies that we defined was for mild to moderate photodamage.

DR. EVANS: Dr. Thorne, you are aware that we are particularly concerned about the prospect of percutaneous absorption of this product and what will happen as a result. This product will be by prescription but, at the same time, it will be perceived as a cosmetic. There is the potential for its use over extensive areas, much wider than would be used for Retin-A in acne. You have given us some data which indicate that there are minimal levels of absorption, even though those minimal levels went up to 8 percent in one case.

You characterized this as an unlikely source of toxicity.

My question to you is, even if it is unlikely, is it possible that such a product, used over a period of time, has the potential for causing embryo toxicity? Is it possible?

DR. THORNE: To my way of thinking, from all the work that I have done, that the Company has done and the people we have talked to, the answer is no.

DR. SCHROETER: The answer is no but in your in vivo studies did you show a cumulative effect of the drug or its metabolites that would indicate a cumulative effect in terms of building up of concentration that would cause a teratogenic effect over a period of time? Because we are not talking about just a short period of time as in your absorption studies; we are talking about long-term use.

DR. THORNE: Well, we had the one study where we actually took patients who had been using it for over a year on photodamaged skin and they really had less absorption than the patients who just used it for 28 days. As you know, tretinoin does not really accumulate in the body. You can take it any way you want to and it does not accumulate. So I think the data are that you do not get above endogenous levels.

DR. SCHROETER: That is very true but we are talking about a cumulative effect on placental products or

embryo.

DR. THORNE: You do not absorb enough of the drug to get above baseline levels -- endogenous levels.

DR. SCHROETER: Dr. Evans, sorry to interrupt you.

DR. EVANS: You did not interrupt; that was my question.

DR. ABEL: As there is no sunscreen in this preparation, if women who use it did not use the sunscreen, how would that affect the absorption and what are the data on how it is absorbed if they were not to use a sunscreen and they had a photosensitivity reaction?

DR. THORNE: Well, since we did not have any experience with patients in any of our percutaneous absorption studies of having sunburns or having any problems with that, which is really a very rare sort of phenomenon, I really cannot answer that, except that I doubt that we would have a problem with absorption. The package insert specifically says that if people do have sunburned skin, they should not really apply it until the skin completely heals. So we do recommend that as part of our labeling.

DR. WILLS: Rob Wills, PRI. Maybe I can lend some additional information on that. Actually, all of our well-controlled studies for percutaneous absorption mimicked what we did in the clinic. So we applied sunscreens and we looked for absorption in that scenario.

The slide I showed with all the literature, the six studies from the literature -- looking through those, none of those studies, to my knowledge, used sunscreen and, yet, our percent absorption was consistent with what was being reported in the literature.

So my guess would be that the sunscreen probably does not make a difference in terms of the absorption of this product from any of the formulations that have been tested to date. I hope that answers the question.

DR. THORNE: The application of sunscreens are, as you know, in the morning. We recommend this be placed on at night and in the morning patients should use a sunscreen and moisturizer. So it is washed off anyway.

DR. WOODLEY: I might have missed this in your protocol book but I know that you had a large number of women in the study that went on for a while. So I am wondering if there have been women who have had children while on the study or were pregnant while on the study, and if you have followed any of the outcomes of those or have any information about that.

DR. THORNE: Dr. Worobec is coming to the microphone to help answer that question.

DR. WOROBEC: Yes, there were three main studies presented and extensions of these studies. So the pregnancies that did occur, occurred mostly during the extension phase,

as you brought out. There were seven pregnancies in these three studies and their extensions. Of these seven pregnancies, three women went on to deliver healthy babies. One woman had a miscarriage between four and a half and five weeks and she had a prior history of a miscarriage at the same time. For one patient we do not have follow up. Two patients elected for personal reasons to terminate the pregnancy.

DR. PECK: I have a number of queries about your percutaneous absorption studies. First of all, these have been done in males only. Is that correct?

DR. THORNE: Yes. Yes, Dr. Wills is coming to the microphone now.

DR. WILLS: Yes, we only conducted these in males because of the radioactivity that we used to administer topically. Giving radioactivity to females is difficult.

DR. PECK: What can you say about the possible differences in percutaneous absorption between males and females?

DR. WILLS: We have no clinical evidence from percutaneous absorption sites to know that, other than one study where unlabeled drug was administered to women for 28 days or so and they looked at endogenous concentrations with the best available methods and could not detect anything, as a matter of fact, in plasma. So those are the best data that

are available.

DR. PECK: Have you considered undertaking in vitro studies?

DR. WILLS: At this point we have not, no. For sex difference? No.

DR. PECK: What was the age range in the males in these studies?

DR. WILLS: It was 19-57.

DR. PECK: In the percutaneous absorption studies?

DR. WILLS: Yes.

DR. PECK: What can you tell us about an age effect on percutaneous absorption?

DR. WILLS: I think the numbers in these studies were fairly small as we were trying to limit the number of people exposed to radioactivity. My summation from those data is that you would not be able to get a yes or no concerning age.

DR. PECK: Richard Guy, at the University of California, has recently published some information indicating a systematic decrease in percutaneous absorption of a number of model compounds. You may want to take that into consideration when you are interpreting your data.

How do you explain the rather significant difference between your studies and that of Tom France? You report less than 2 percent absorption, whereas, Dr. France reports 5-7

percent.

DR. WILLS: If you look at our combined absorption, feces and plasma, it was somewhere over 2 or around 2 percent. I think sometimes when you are dealing with those small percentages and those levels of radioactivity, that is experimental error, in my opinion.

DR. PECK: That would not lead us to have much confidence in any of your data if you think that you cannot distinguish between 2 percent and 7 percent.

DR. WILLS: Well, some of the other studies in the literature are down to less than 1 percent total recovery and some went up as high as 8. So there is quite a bit of variation across all the literature, including our work. But they are consistently in the low percentage absorption range.

DR. POMERANZ: I was wondering if the fetuses that were aborted, either spontaneously or electively, were studied pathologically for any evidence of abnormalities.

DR. THORNE: Not that I am aware of.

DR. NIEBYL: How could you study it in five weeks?

DR. SCHROETER: Could you identify yourself, please?

DR. NIEBYL: I am Jennifer Niebyl. I am an obstetrician. I am saying if someone has a miscarriage at five weeks, you cannot find a fetus to study for pathological abnormalities. You might be able to look at tissue levels in some other country, as in that New England Journal article

but it is too early to look at the fetus for morphologic abnormalities.

DR. POMERANZ: Did they say that they were all at five weeks? What were the ages involved?

DR. WOROBEC: The spontaneous miscarriage was at 4.5-5 weeks. There was identify of embryonal tissue made. In the 2 women who elected for personal reasons to have termination, we do not have the follow up because these were personal decisions of their own.

DR. STEIN: I am also concerned about the differences in absorption reported by different investigators. Obviously, there are some problems with the methodology and there may be a statistical problem in detecting very small differences. But have you looked at people with disorders of keratinization that may have a disrupted epidermal barrier without inflammation? That may potentially serve as a good model for looking at absorption.

DR. THORNE: We have not really formally tested that. We have gotten blood levels from patients who have had lamellar ichthyosis and other things, who have actually used Retin-A all over their bodies, and we were unable to detect tretinoin in their blood. Of course, that is fairly sensitive, at least down to 2 ng. Tretinoin is absorbed about 1-2 percent, no matter what you do. As long as you have stratum corneum there, it seems to block it. We have <u>in vitro</u> data

which really correlate what we have in vivo.

Additionally, the study that Dr. Wills reported on was actually on 42 patients, which is a very large study, and everything in that study was consistent. So that was a large patient population.

DR. STEIN: That is exactly the kind of thing that I think needs to be done. Do you just have one or two patients or --

DR. THORNE: With ichthyosis?

DR. STEIN: Yes.

DR. THORNE: I think we did it on two patients. We do not have that large a population. We could certainly think about doing that.

DR. STEIN: Yes, I think that would be ideal. It would be methodologically difficult but it would be ideal to try to account for as much of the drug as you could overall.

DR. SANDERS: John Sanders, medical officer at the FDA. At the NIH symposium about a year ago, many in the audience mentioned the word edema as a result with Retin-A. Have you had any post-treatment analyses with these patients to show that this therapy is not associated necessarily with edema?

DR. THORNE: We have one slide that might summarize the effects with people who stopped therapy, because that is a question that was asked at one Advisory Panel previously --

what happens when you stop patients, which is very difficult to do, I might add. It is very hard to stop patients using Retin-A or Renuva, in this case.

(Slide)

This summarizes a group of patients who were treated for 12 months with Renuva and then either stopped or they applied it once weekly or they applied it 3 times weekly. This is after 6 months. These are preliminary data. Unfortunately, we do not have the complete time frame. But essentially 49 percent of the patients maintained the improvement they had after 1 year of topical Renuva therapy; 44 percent worsened; 7 percent improved a little bit. If they applied it once a week, they could maintain this improved state to a higher level. If they used it 3 times a week, they got more improvement, better maintenance and substantially lower degree of worsening. This is after 6 months after stopping the material.

So, again, this is good affirmation of the fact that irritation probably does not play a major role in this.

DR. SCHROETER: Dr. Thorne, I have a particular question that I think is important. It is assumed that your labeling will be for therapy of photodamaged skin. Among the parameters included in photodamaged skin is epidermal dysplasia or keratinocyte dysplasia or atypia, as you have given both terms, and melanocytic atypia. Your biopsies

showed thickening of the epidermis and normalization of the cornified layer and thickening of the collagen and ground substance in the dermis. But I saw no data whatsoever to support the contention that you have eliminated atypica or epidermal dysplasia that is associated with actinic keratosis. If, indeed, there are no data, then I do not think you can use this in your labeling.

DR. THORNE: The group of patients that we selected really did not have actinic keratoses. They did not really have much keratinocytic atypia, which were interested by. We thought that if we biopsied patients they would have a fair amount of microscopic atypia, even without visible actinic keratoses. But that does not seem to be the case. So the reason we did not change it very much is because there was not really very much there to begin with.

DR. SCHROETER: Well, this is an extremely important public health concern because we have the primordial lesion of squamous cell carcinoma incurred in actinic keratoses and what is implied by improving or therapeutically affecting photodamage is to eliminate this progression. In fact, to the contrary, although it is a different model system in xeroderma pigmentosum, recent studies show that using Retin-A topically or another retinoid internally, and we assume that it will give some comparable effect, only suppressed possibly the occurrence of squamous cell carcinoma, basal cell

carcinoma, as well as melanoma. There is another study that was given at the AAD, a poster last September, that showed that possibly we were only suppressing atypia in the epidermis of patients who had significant dyskeratoses beforehand. So I think that this has to be approached before you can make that labeling. Dr. Peck?

DR. PECK: I am a little concerned about your characterization of the last Committee meeting discussion of this. As you know, this was a closed meeting. So at the moment the transcript is not available for public scrutiny.

My recollection of the discussion of the safety matter was very different from yours. It was a rushed discussion. Significant safety concerns, particularly regarding cutaneous metabolism, systemic absorption, accumulation in the fetus, teratogenicity and so forth, were expressed and I believe there was a consensus that there was a very inadequate data base available to make that assessment.

I wonder if you want to stick by your fairly rosy and optimistic characterization of that or if you would like to give us permission to release the transcript for public scrutiny. Just how would you like to interpret that now?

MR. OHYE: Ohye, R.W. Johnson Pharmaceutical Research Institute. We believe in regulation in "sunshine". So if the Agency would like to release the transcript, would have no objection.

DR. FLEISS: We began discussing the biopsy results. One of the questions posed to us is how do biopsy results compare to other outcome measures in importance? This morning is the first time that we were presented any data at all concerning the biopsies.

DR. EVANS: Let me say, Dr. Fleiss, that one of the reasons that you have been presented more data on the efficacy aspect of it is because the FDA staff has not finished the review of the efficacy analyses for this product. We wanted to make sure that the parameters that we were discussing were, indeed, the most important ones and how to relate one with the other. We did not want to give you the efficacy data from our perspective until they are in.

DR. SCHROETER: Dr. Hulka, do you have any questions regarding the issues, or your Committee?

DR. HULKA: I do not.

DR. SCHROETER: Do any of the members of the Fertility and Maternal Health Drugs Advisory Committee have questions that they want to address to the R.W. Johnson Company and their IND proposal?

DR. SCHLESSELMAN: Jim Schlesselman. I would like to go back to the issue that Dr. Peck was raising earlier about the absorption of radiolabeled topical tretinoin and ask for a clarification of the dosing that was done in the studies of absorption; for someone also to address the matter

of factors that are known or suspected to affect the absorption of such a drug and address the question of what was done in the design of the studies to control for these factors; finally, to talk about what are likely to be the extremes of dosing to occur in practice and how extremes of dosing were accounted for in the studies that we had a glimpse of today.

DR. WILLS: Rob Wills, PRI. You had quite a few questions there, if I could ask you to repeat the first one, I will start from there.

DR. SCHLESSELMAN: Why don't we start with factors that are either known or suspected to affect the absorption of this drug?

DR. WILLS: Percutaneous absorption?

DR. SCHLESSELMAN: Yes, that is right.

DR. WILLS: In our study that we ran for percutaneous absorption, we basically controlled for photoexposure which we know can affect absorption since you can have photodegradation. These people were classified as having photodamaged skin. So we know that with abraded or severely compromised skin you can affect absorption. In this case, these people were typical of what we planned to treat for the indications.

Other factors that might affect the percutaneous absorption of products would largely involve the integrity of the skin or concomitant ointments, creams or things you may

put on that would act as a second barrier. In our studies, those were not available or we did not use those and we controlled our skin. That is about what we can say concerning our studies.

DR. SCHLESSELMAN: So the conditions under which the tests were done would not be likely to represent the extremes under which the drug might be used in actual practice.

DR. WOROBEC: In a 28-day pretreatment group we actually had patients come in every evening and we had nurses apply the medication to the facial area, just to be assured that it was being pretreated for 28 days because the issue comes up of factors that may affect percutaneous absorption and one is any irritation. So we wanted to see, in the face of this, by controlling the application, what the absorption would be. So we did the best we could to make sure it was being applied; that we were seeing what would happen in the face of this retinoid response as well.

DR. NIEBYL: It seems that a very similar product, Retin-A, has been on the market for quite a long time. Could you review the pregnancy experience with patients who used Retin-A in early pregnancy? The last time we reviewed this, we had no evidence of teratogenicity.

DR. THORNE: Yes, and the same is still true. Over approximately 20 years that Retin-A has been used in the

treatment of acne, there have been approximately 8 instances of pregnancies which had an outcome of fetal abnormalities, with mothers who had been using topical tretinoin. That is approximately a million pregnancies and about 9 (sic) examples. So it is not --

DR. NIEBYL: So it reduces birth defects!

DR. THORNE: We do not go that far. None of the fetal abnormalities resembled those seen with other retinoids.

DR. SCHROETER: We have time for maybe one last question. Dr. Woodley?

DR. WOODLEY: I wanted to ask if you were able to analyze the subjective data with the biopsy results and image analysis results to see if there is a correlation. I know you did correlation between studies but actually in a few individuals, like in individual A, did the subjective evaluation of individual A correlate with the objective parameters of improvement? Or was there some discordance in that? You had a lot of patients. So you would maybe need to do only a handful of them to make sure that there was concordance between the subjective and objective evaluations.

DR. THORNE: The way these studies were designed, we really could not do that because the biopsies were taken from a very, very small part of the skin while the clinical signs came from the entire face. So it was very difficult to correlate exactly what was happening in the biopsy with what

the clinicians were seeing. The studies were not designed to answer that particular question.

DR. WOODLEY: But did you look? I know they were not designed that way but, let's say, Betty Lou had subjective evaluation by herself and by an investigator and showed improvement, what happened with her biopsy and what happened with her image analysis results?

DR. THORNE: The best association was with melanin pigmentation. Those patients who had decreases in melanin did, indeed, have a decrease of melanin in their biopsies. So that was about the best we could really correlate using the histologic techniques. But, again, the studies were not really designed to pick that up.

DR. SCHROETER: At this point, I would like to focus the Committee's attention to the questions that have been constructed by the FDA. These include the questions that are in the material that you received, dated May 3, 1990.

The first question: Efficacy parameters used in the evaluation of this product by the sponsor are -- and let's just go through these in a systematic fashion. I want to remind you that this drug is not being considered in terms of its labeling. Labeling has not been produced or submitted. But the FDA is asking this Committee to evaluate the parameters that they have listed here and that the Company is

using to support their thesis of eventual labeling for efficacy and safety. I think that is as succinct as it can be at this particular time.

So let's start at the top:

- Changes in the signs of photodamaged skin reported by the investigator. Are these appropriate? Are these equally important? -- all of these, but I think we should go down the list.

No comment? Then you feel that all these -- changes in skin characteristics reported by the patient; biopsy results; skin surface replica analysis results -- all of these are really important? Yes, Dr. Stein?

DR. STEIN: Do you just want to call each person individually?

DR. SCHROETER: Sure, if you wish. There may be no comment. I presume that if you are silent, that is consent.

DR. STEIN: No. No, I would like to comment.

DR. SCHROETER: Dr. Stein?

DR. STEIN: I am really concerned about the subjectivity of (a) and (b) at least. I am wondering if really in future more emphasis should not be placed on the skin surface replica analysis. I think the methodology needs further developing but, as I said, I think it has a lot of potential.

I am wondering if there is not some way to use that

technique to actually measure the area; to somehow integrate the curves that are being looked at; to measure the total area and somehow develop a statistical test of that. I just cannot answer that.

DR. FLEISS: It is the patient's subjective complaint that brings the patient in for care. I would put the patients' responses, subjective as they are, as number one. If we need larger sample sizes to overcome the variation that produces, so be it. But I would put the patient's report as number one; investigator's report as number two; the skin surface replica results as number three. I do not have the foggiest idea what the biopsy results are like. So I cannot put that anywhere.

DR. ABEL: Well, I agree that (a) and (b), the subjective evaluation by the investigator and the patient, are very important. In regard to the biopsy results, I would like to see some information on the patients for whom this is going to be widely used, and those are the severely photodamaged elderly patients on whom these studies did not focus. I would be interested in the skin surface replica analysis results.

Getting back to the biopsies, the question of what the effect is on the epidermal dysplasia and melanocytic dysplasia is important.

DR. SCHROETER: Dr. Pomeranz, any questions or

comments?

DR. POMERANZ: No.

DR. SCHROETER: Dr. Tschen?

(No response)

Dr. Woodley, any additional comments?

(No response)

I think that all of these are equal. If they are equal, then they all have to be answered. I feel that the techniques are new but I think that they do represent a significant evaluation, not only subjectively, which I think you have obtained, but the new technique of modeling in terms of electronically evaluating does give you some objective numbers to hang on to and I think that is good and the skin surface replica analysis should be pursued.

I am concerned about two things: One, the biopsy results, as I have expressed my concern before and as Dr. Abel has, you population group does not answer the question of whether you are therapeutically and prophylactically going to deter the continued occurrence of actinic keratoses or keratinocyte dysplasia and melanocytic dysplasia or atypia by the use of this compound. Until you answer that, I do not think that you can label it as being therapeutic in those parameters.

That leads me to the final item. You must have more patients in the severely actinic damaged group, whether

they be aged or not. It would be presumable that you would get more aged patients and, therefore, get more severe photodamaged skin than what you have at the present time to evaluate.

DR. BILSTAD: Jim Bilstad, FDA. I just wanted to comment on the subjective parameters. Obviously, there are many situations in which we use subjective parameters in clinical studies, usually rated on some sort of scale. They become a particular problem when blinding is a problem. I guess I would raise the issue here. How convinced are we that the blinding was complete here? Could erythema induced by the drug have basically unblinded the study?

DR. STEIN: I want to echo that because, you know, perhaps the subjective question is a more important question but the reason I am raising it is also in relation to how well it can actually be blinded.

I would like to ask a tangential question. Also I assume or I suspect that you the 0.25 concentration and, if you are not, do you intend to do that?

DR. SCHROETER: Does somebody from the Johnson Company want to answer that question?

DR. THORNE: The NDA that we are discussing today is Renuva at 0.5 percent tretinoin emollient cream.

DR. SCHROETER: Dr. Hulka, do you or your group want to make any comments regarding the first question here?

Are these parameters equal in terms of their use and evaluation?

DR. HULKA: Well, I would only echo the point that if these were truly blinded trials and if, particularly, the subjects were blinded and, of course, the investigators, then I agree that the subjective reaction of the subject is the most important outcome and, secondly, the investigator's reaction. But the issue here is blinding.

DR. SCHROETER: Does anyone else on the Panel want to make any comments? Dr. Woodley?

DR. WOODLEY: I think you have to say that at some level, at least, this study could not possibly be totally blinded. I think what you see in the results really reflects that. You see that the investigators feel subjectively that there is a little better improvement than the patients, who feel that there is an improvement but not to the same degree as the investigators. That is a little bit unlike most studies that are blinded. Usually patients hope against hope and their subjective evaluation is a little better than the investigator's evaluation.

I think what happened in this study is that there was some mild erythema and some of the typical topical effects of tretinoin. That resulted in the investigator being able to know who was and who was not on the drug. That little bit of erythema was perceived by the patient a little

bit as a negative. That is why I think the patients did not respond as positively as the investigators because they had a little topical tretinoin effect on their face and that was perceived a little bit as a negative. I suspect that is what happened.

DR. SCHROETER: Would you identify yourself?

DR. NIGRA: Tom Nigra. I am one of the clinical investigators who did this study. David, I can tell you in practicality how we did it. We had 100 patients. We had those early side effects and, yes, I think that some of the erythema that occurred in some of those patients was a little more than occurred on the vehicle. We had at least 2 concentrations of drug, high and low concentrations, and both of them produced erythema.

Six months later -- I do not remember patients that well, not 100 patients -- that patient came in. We had the photographs. We had the patient. We did our global evaluation at that time. I, personally, did not look back to find out if they had erythema early on. I could have done that. But from my point of view, as an investigator, that would have put a bias in and so I did not do that.

DR. PECK: I would like to pose a question to our two statisticians, Dr. Fleiss and Dr. Schlesselman. The use of the sequential Bonferroni procedure -- this particular procedure is new to me and, in fact, counter-intuitive,

although I do notice that there are two citations, one in the Scandinavian Journal of Statistics, and one in a book on multi-comparisons. So, conceivably, this is quite legitimate. Would you comment on your reaction or your judgment as to the appropriateness of this particular procedure as applied here?

DR. FLEISS: It is relatively new to me. I have seen references to it in the literature. I have never used it. This is the first time I have actually seen it applied to real data.

What I did, frankly, was to apply the multiple comparison procedures I am familiar with and experienced with to these same data and I came up with exactly the same results. I have to look more carefully at the procedure to really comment on its validity but, on the face of it, it seems all right.

DR. SCHROETER: Dr. Schlesselman?

DR. SCHLESSELMAN: Well, I place more stock in the replication of the findings across the three centers than I do in any test of significance that is done on the bases of any one procedure, however cleverly devised. So to me what is important is the consistency of the findings across centers, rather than the significance or lack of significance found within any one center. I really am not one to think that there is much of a multiple comparisons problem here

with the data as they have been presented. So whether adjustments are made to account for multiple comparisons or not really would not affect me one way or the other.

DR. SCHROETER: Let's move on to the other portion of the question: Should other endpoints be considered? We have addressed that to a certain extent in the discussion. Are there any comments regarding should other endpoints be considered?

If not, I will move on to the second question: In consideration of the demonstrated absorption of tretinoin through the skin, its fetotoxic capability in animals and the observation that human exposure to 13-cis-retionic acid (Accutane) results in high placental and embryonic concentrations of tretinoin, how should the safety concern of prolonged use of this product be approached?

Is there anybody on the Panel who would like to address this issue as related to the New England Journal article, 1989?

No comment from the Fertility and Maternal Health Drugs Advisory Committee? No comment? Dr. Thorne, would you like to address this question?

DR. PECK: I am not sure you are giving the Panel enough time to react. I see at least one possible response over here.

DR. SCHROETER: Dr. Abel?

DR. ABEL: This is not a question as far as the indication for photo-aged skin, but it is a question regarding the possible use and total body use in, say, conditions such as lamellar ichthyosis. I would be interested in further data on percutaneous absorption in widespread use but I know that is not the proposed indication for this new form of Retin-A.

DR. EVANS: What we were getting at was patients who might require, due to photo-aged skin, wide areas of treatment with this product, with the potential for absorption. So the question was whether you foresee a possible safety problem and how should this whole thing be approached?

DR. ABEL: Well, patients who have had long-term PUVA have widespread aging effects due to the PUVA therapy. So that could possibly be a potential for wider use over a larger part of the body than just the face.

DR. STEIN: In addition to patients with ichthyosis and other disorders of keratinization, you might want to look at patients with very extensive acne -- I do not know if that has been done -- who are applying it to much of the area of the trunk and somehow getting absorption in that fashion. This is an important question which, obviously, needs a lot more data before we can get a better answer.

DR. SCHROETER: Yes, Dr. Thorne?

DR. THORNE: Some years back we did do a study

where we actually took volunteers and covered them almost from head to foot with Retin-A, in this case 0.25 percent, and using the best technology that was available at that time, we could not really measure plasma levels in any of these subjects. So, again, even with widespread application, you cannot get above an endogenous sort of level and, again, in our application we are stressing facial application. We are not looking for total body use at all. I do not know of any physicians who recommend Retin-A for total body use or patients who would really want to undergo total body use with Retin-A.

DR. STEIN: I understand that and that is a fair point. But the methodology available today, I think you would agree, is more sensitive than it was 15 years ago or 20 years ago, whenever those studies were done.

DR. THORNE: Ten years ago.

DR. STEIN: Ten years ago, sorry. And I think it might be worth looking at higher concentrations also with widespread application, the 0.1 percent lotion.

DR. THORNE: Those would be cold studies and we would have to calculate how much we think we could find in the blood over background. When background is 2-5 ng/mL, it is hard. You would not be able to know which is coming from the Retin-A and there is a lot of diurnal variation. So there are a lot of technical questions to what you are

asking. That is why we used cold studies. Again, they are very indicative of what is happening in the clinical condition.

DR. WOODLEY: Maybe I am missing it here but I really think that I am persuaded by our long use of topical tretinoin for a variety of conditions, including keratosis pilaris and widespread acne. It has been out there for a number of years. I think the safety studies presented here are very consistent with safety studies that have been done in the past and I really think that although this is an important issue, it has been resolved by many, many years of clinical experience with a very similar medication. Now we have their studies which just sort of mimic previous studies.

So I would say overall that, to me, the efficacy issue in a way is almost more interesting than the safety issue, although the last issue is really more important. But I think that this is going to be shown to be relatively safe.

DR. PECK: I think we are somewhat compromised by not having had an FDA presentation that presents some of the toxicological and biopharmaceutical considerations that are being brought to bear on this. Dr. Schlesselman's question relating to factors affecting percutaneous absorption actually was quite perspicacious. There is a long list of factors that affect the absorption that I am sure the dermatologists on this Committee are perfectly aware of.

They include sex, age, body site, photoexposure, vehicle occlusion or lack of occlusion, barriers, enhances, etc.

What we have seen presented this morning is a very minimal subset of the various conditions under which widespread availability of this agent could be used. It is well-known that absorption on the forehead, face and neck are very high absorption areas. Yet, the studies have been restricted to selected portions of the face in males. So we do not know if there is a 15 percent absorption or 7 percent or 2 percent in females.

We have heard nothing about the cutaneous metabolism of this. We have heard the concept that the presence of a sunscreen -- we have heard that called a barrier. Actually, it could be an enhancer. We know that a number of mosquito repellents produce a significant movement of a variety of chemicals. So I think that our concerns are from satisfied from widespread use of a different formulation. Remember, formulation effects are very important.

I think I will leave it at that but we should have, I think, for the purposes of this discussion presented more of the concerns that have arisen about the biopharmaceutic, toxicological concern on the part of the FDA staff.

DR. WOODLEY: They did address one of the major permeability problems, that is, inflammation. We know that inflammation will dramatically increase absorption. The

purpose of their study was to enhance inflammation with drug before applying the labeled drug.

Going back to what this drug has been used for in the past in other formulations, I think that is a valid point, but it has been widespread inflammatory disease, namely, acne, which is an inflammatory disease. So of all the things that influence permeability barriers, I would think inflammation and compromise of the skin barrier itself is one of the greatest.

DR. SCHROETER: I think that that concludes our discussion of the tretinoin emollient cream. We will adjourn for a break. I think we are due to be back here from our coffee break at about 10:45. Thank you.

(Brief recess)

DR. SCHROETER: We will reconvene. We will now address the Accutane issue, NDA 18-662. We will have introductory comments by Dr. Robert Nelson, from the Accutane Monitoring Group at the FDA.

INTRODUCTORY COMMENTS BY ROBERT C. NELSON, Ph.D.

DR. NELSON: One thing I did place on the table while you were away is the boxed warning section of the current product labeling. I will be referring to that in a few moments in my presentation. So you might pull that out and keep it handy.

This morning I have been asked to introduce one of

the most difficult regulatory issues that the FDA has ever faced. Then I will attempt to set the stage for the more detailed presentations which are scheduled to follow.

Those members who were on the respective Committees for the May, 1989 and the June, 1989 meetings when Accutane was on the agenda received full background presentations at those sessions. In addition, you have all been supplied in your mailings with a detailed Accutane chronology from 1982 through 1988.

My mission today is to briefly review for you the public health situation that existed prior to the May, 1988 interventions; identify the goals and the intentions of those interventions; outline in general what those interventions were; update you on how and when they were implemented; explain FDA's Accutane monitoring activities and list FDA's current concerns.

I will speak in general terms, leaving the specific details to speakers from the firm and from our Office of Epidemiology who are to follow. Hopefully, when I am finished we will have set the stage for the agenda topic on Accutane.

In April of 1988, a landmark Dermatology Advisory Committee meeting was held during which data on the extent of Accutane use in females of childbearing potential were provided. Data on the national estimates of the incidence of

severe cystic acne recalcitrant to other therapies were provided. Data on the estimated pregnancy exposure to Accutane since its 1982 marketing were provided. Data on both the reported and the estimated Accutane-induced birth defects since its 1982 marketing were provided.

Much of these data were discussed with great vigor, controversy and emotion. Consensus on the magnitude of the Accutane teratogenicity problem was not reached. However, there was a consensus that a substantial and important public health hazard was present and that strong, definitive steps needed to be taken to minimize, if not totally eliminate, the risks of pregnancy exposure.

Shortly after that Advisory Committee meeting, on May 15, 1988, the FDA issued a regulatory letter to Roche which specified an intervention with seven areas of required action. These included:

- one, extensive revision of the physician package insert;

- two, understandable patient labeling;

- three, radically revamped packaging;

- four, written informed consent form;

- five, educational programs for both physicians and patients;

- six, a surveillance study to assess the impact of the preceding interventions;

- seven, other epidemiological surveillance efforts by Roche and by FDA's Epidemiology Division.

The two goals of these interventions were, one, to reduce prescribing to levels consistent with the epidemiology of severe cystic acne in the population at risk and, two, to eliminate pregnancy exposures in women prescribed Accutane, thereby, eliminating the associated adverse outcomes.

In response, Hoffmann-La Roche launched a pregnancy prevention campaign that could easily be called the most extensive educational and relabeling effort ever attempted for any prescription drug. As part of their presentation, the sponsor will, I am quite sure, provide you with a full description of this intervention program. However, I will highlight a few of the most important components and let me now refer you to the boxed warning on the label:

The professional labeling for Accutane now states that Accutane is contraindicated in women of childbearing potential unless the patient meets all of the following conditions:

- one, has severe disfiguring cystic acne that is recalcitrant to standard therapies;

- two, the patient is reliable in understanding and carrying out instructions;

- three, the patient is capable of complying with the mandatory contraceptive measures;

- four, the patient has received both oral and written warnings of the hazards of taking Accutane during pregnancy and the risk of possible contraception failure and has acknowledged her understanding of these warnings in writing;

- five, the patient has had a negative serum pregnancy test within two weeks prior to the initiation of therapy and it is also recommended that pregnancy testing and contractive counseling be repeated on a monthly basis;

- six, the patient will begin therapy only on the second or third day of the next normal menstrual period.

Clearly, the intent of the first qualification was to eliminate excessive use by limiting the use of Accutane for those females with severe cystic disease. Then, through the diligent use of Roche's pregnancy prevention kit, qualifications two through six were to be attained and pregnancy exposures prevented.

A second important component of the intervention was a broad array of educational campaigns which were put into effect to inform Accutane prescribers of these new data and to discourage use outside the labeled indication. It should be noted that Roche, to their credit, has not used positive detailing since the start of the program.

Thirdly, in a revolutionary move, Accutane was made available in packs of 10 in the unique blister-pack. An

example of that was in the package that Roche submitted to you prior to this meeting.

Then in an attempt to assess the impact of these interventions and to understand what was actually occurring in the marketplace, Roche contracted with the Slone Epidemiology Unit from Boston to conduct an intervention assessment study. The value and the limitations of this effort will be discussed thoroughly later this afternoon.

This complex set of interventions, as could be expected, were not easy to implement. Some examples of the difficulty were some early miscommunications between FDA and Roche. A consequence of one of these miscues was the fact that the enrollment form for the survey was not placed in the initial pregnancy prevention package during its first detail wave.

There is some lack of agreement over the methods used in the Slone study and a delay, for a variety of reasons, in introducing the blister-pack until May of 1989, one full year after it was requested. It is hard to hold Roche responsible or hold Roche at blame for this. It was a difficult transition with many complicated factors.

Because closer interactions were felt to be vital, added to the legitimate plea from the sponsor to receive only one set of instructions from the FDA and a need for active surveillance of this important issue, Dr. Bilstad created the

Accutane Monitoring Group, the AMG as I will refer to it, six months later, in November of 1988. The AMG is composed of three members, Drs. Carnot Evans, Phylis Huene and David Bostwick from the Dermatology Division of Anti-Infective Drug Products and three members, Dr. Chuck Anello, Bruce Stadel and David Graham, from the Epidemiology Division. At that time, holding the position as Dr. Bilstad's assistant director, I was appointed as chairman.

The major functions of the Accutane Monitoring Group were to facilitate internal communication and coordination on this issue and then, first, to define the contents of the quarterly reports that we requested from Roche, and then to review each report within two weeks of their receipt; to hold quarterly meetings with Roche and their contractor to discuss the progress of this multi-faceted intervention program and, lastly, to provide quarterly updates and briefings to FDA's policy level.

Each quarter Roche would submit a report with the following contents: Adverse reaction reports on pregnancy exposures and their outcomes; drug use estimates and manufacturing distribution data; current status, progress and enrollment into the impact assessment study; all advertisements and educational campaigns so that we know what components of the intervention program were reaching whom, when and how often.

At this point, I feel it is important to make note of Roche's diligence in negotiations and fulfilling its commitments and, to the extent possible, meeting the time frames that we set. It was truly a massive undertaking.

I want to close my briefing by reviewing FDA's current concerns. They are the continued high level of Accutane use in the population at risk; prescriber non-compliance with vital components of the program, both of which increase the probability for pregnancy exposure and its range of adverse outcomes. In addition, we are concerned with relatively low enrollment in the impact assessment survey and that fact leaves us with the inability to rigorously assess the occurrence of pregnancy exposures and the inability to rigorously assess congenital defects.

A set of official questions has been prepared for Committee discussion but I will paraphrase them very briefly here: Has the pre-1988 adverse public health situation changed in a meaningful way and to a meaningful extent? I will stop there. Thank you.

DR. SCHROETER: Let's continue with a review of data by a representative of Roche. Please identify yourself.

PRESENTATION BY ROBERT B. ARMSTRONG, M.D.

(Slide)

DR. ARMSTRONG: My name is Robert Armstrong. I am the director of medical affairs for Roche dermatologics.

Joining me today is an associate, Dr. Wanju Dai, who is the director of pharmacoepidemiology and the department of drug safety.

(Slide)

I would like to stress at the outset that we in no way minimize the seriousness of the birth defects that are associated with Accutane exposure during pregnancy. As an indication of the seriousness with which we hold these birth defects, we have provided support in terms of information, publications and even financial support to continue the ongoing study of these malformations. In fact, this afternoon you will hear presentations by Drs. Lammer and Adams which were funded through a grant that is administered by the Massachusetts General Hospital.

The situation of birth defects is doubly tragic because there is the potential theoretically to completely eliminate these birth defects through either of two mechanisms: One mechanism would be to have the patient avoid the use of Accutane. The second would be to avoid the use of Accutane during pregnancy. It is this goal of avoiding pregnancy that we have concentrated our efforts on to achieve.

(Slide)

Before I proceed to discuss other aspects, I would like to make a brief mention of the benefits of this drug.

Severe recalcitrant cystic acne is, in fact, a serious disease. It produces painful lesions that run a very chronic course. In the pretreatment era, as you heard this morning, it was not unusual for patients to have this difficulty for periods of five, ten and even more years.

Typically, these cases responded poorly, if at all, to other forms of therapy, including oral antibiotics, sometimes hormonal therapy and sulfones that might be attempted, all with varying and, unfortunately, typically limited benefit.

So I think it is fair to say that Accutane is the first extremely effective drug for the treatment of severe recalcitrant cystic acne. In fact, it is the only drug which can be construed to control and cure most cases. Results are typically produced in the recommended 4-5-month treatment period and remissions are usually prolonged, apparently indefinitely in some patients.

(Slide)

I would like to give you one example of a patient to illustrate the degree of discomfort and also the potential for social, emotional and occupational disability that could be associated with this disease. This is a patient before treatment, and you can appreciate the difficulty he would have in going through life.

(Slide)

At the end of a course of Accutane treatment, the same patient clearly looks substantially better, although you can still detect traces of scarring from lesions that had been destructive of facial tissue before his treatment period.

I would now like to ask Dr. Wanju Dai to discuss the reports of pregnancies.

PRESENTATION BY WANJU S. DAI, M.D.

(Slide)

DR. DAI: Good morning. I am going to present to you an overview of the Accutane exposed pregnancy reports that were voluntarily reported to Hoffmann-La Roche.

(Slide)

This slide is very similar to a slide that we submitted to you for your review that is enclosed in your package. The only difference is that this slide is more current than the one contained in your package.

As of April 30, 1990, we have received a total of 483 pregnancy exposure reports. This table is done by pregnancy outcome and by the year of commencement of Accutane therapy by these women.

Based on Accutane use data that we have received from PDS, I have calculated the reported pregnancy rate by year of commencement of Accutane therapy. For example, in 1983 there was a total of 109 pregnancy exposure reports.

This resulted in 10 pregnancy exposures per 10,000 women who were between 12-44 years old and were exposed to Accutane. As you can see, the reported pregnancy rate was the highest in the first 3 years of marketing and declined about 50 percent from 1984-1985.

The current reported pregnancy rate is approximately 6 pregnancy exposures per 10,000 women of childbearing age. There is a total of 86 congenital malformation reports. These include 8 congenital malformation cases that were detected from abortuses and 4 cases from stillborn infants.

The number of congenital malformation reports peaked in 1983. Even though there was a high level of public awareness of Accutane's teratogenicity, we have received a total of 6 birth defect reports from the voluntary reporting system in 1988 and 1989. Based on PDS data, it was estimated that approximately 130,000 women of childbearing age were exposed to Accutane therapy in 1988 and 1989 combined. There were 4 infants with congenital malformations who were reported to be born in 1989 and 1 infant with malformations was born in 1990.

(Slide)

As a physician and as an epidemiologist, I think it is imperative to find out the causes of these pregnancy exposures. Therefore, I evaluated those cases that were voluntarily reported to us where maternal exposure to

Accutane was commenced after January 1, 1989. I chose this time because this is the time when our pregnancy prevention program was partially implemented. There was a total of 43 cases. The information on the timing of conception in relationship to Accutane therapy was available on 37 of these 43 cases. More than 90 percent of these women were at least verbally counseled by their physicians to avoid pregnancy during Accutane therapy when Accutane was prescribed.

The causes of the pregnancy exposures are listed on this slide. There were 5 patients who were self-treated. This means that these women used leftover Accutane capsules to treat themselves without awareness of a physician. To our knowledge, all these women had used Accutane capsules that were purchased prior to the implementation of Accutane's blister-pack. There was a total of 8 patients who conceived prior to Accutane therapy.

As you can see, the majority of these pregnancy exposures occurred during Accutane therapy and 18 patients conceived during Accutane therapy while practicing contraception. These pregnancy exposures occurred either because of contraceptive failure or due to patient unreliability. In addition, there were 3 patients who claimed to be abstinent.

In summary, we continue to receive pregnancy exposure reports. The magnitude of the reporting indicates that physicians and other health care professionals are still

very conscientious in reporting pregnancy exposure cases to us although this medication has been on the market for more than 7 years.

As you are aware, Accutane has been a highly visible product in the past two years. Even with this being the case, we have received a total of 6 spontaneously reported birth defect reports where maternal exposure to Accutane was commenced in 1988 and 1989 combined and it was estimated that approximately 130,000 women of childbearing age commenced this therapy in these 2 years. The majority of patients having pregnancy exposure to Accutane was due either to contraceptive method failure or due to irregular use of the contraceptive method. In addition, 13 percent of the patients were self-treated with leftover capsules without the awareness of the physician.

I believe the best way to prevent this pregnancy exposure is through education, both on the part of the physician and the patient. Thank you. Now I will turn the podium back to Dr. Armstrong.

PRESENTATION BY ROBERT B. ARMSTRONG, M.D.

(Slide)

DR. ARMSTRONG: I would now like to discuss usage. We do not have absolute numbers on how many women between the ages of 12-44 use Accutane but we are able to use commercially available data bases that project the use of this drug.

These numbers are presented to you for 1983, the first full year of Accutane's availability, through 1989.

The blue bars represent the projected number from this system and the red triangles and yellow squares represent confidence intervals above and below that projection. The width and overlap of these confidence intervals makes it impossible to judge the statistical validity of differences from one year to the next but the downward trend in the confidence limits is statistically significant over the period from 1983-1989.

Frankly, we were surprised to see that the usage of Accutane in 1989 was not noticeably different, certainly not dramatically different from what it was in 1988. This was in contrast to the reports -- although anecdotal reports, they were numerous -- from professional representatives as they made calls to physicians. We consistently heard that physicians were using less of the drug. So we have attempted to find out if there might be some changes occurring that were not being reflected within the wide confidence intervals of these projections.

(Slide)

At this point I would like to introduce Dr. Brian Strom, Associate Professor of Medicine and Pharmacology and Co-Director of the Clinical Epidemiology Unit at the University of Pennsylvania, to discuss what he has done on the

usage of this drug.

PRESENTATION BY BRIAN STROM, M.D., M.P.H.

(Slide)

DR. STROM: What I will be presenting to you is a summary of work in progress, summarizing the current status of the results of two different studies that we are performing.

(Slide)

The first is looking at trends in Accutane utilization. The second is looking at rates of exposure in pregnancy and outcomes following Accutane exposure in pregnancy.

(Slide)

Both of these studies are based on data from COMPASS, the computerized on-line Medicaid pharmaceutical analysis and surveillance system, a commercial data base developed by Health Information Designs, Inc., based on Medicaid MMIS billing data and including information on demographics, outpatient drugs, inpatient and outpatient diagnoses, procedures and deaths.

(Slide)

Our first study was done to evaluate trends in the utilization of Accutane.

(Slide)

We looked at all COMPASS data sets which included

Accutane. This included 4 of the Medicaid data sets, Arkansas, Florida, Michigan and Minnesota, and 2 of their non-Medicaid data sets which we refer to as client N and client Z for the purposes of confidentiality. One is a major state employee group which has all of the employees of this major state, and the other is a major non-governmental employer and all of their employees.

(Slide)

It is important to note the Accutane prescribing restrictions which were present in some of these states. In Arkansas, in fact, Accutane was never formally covered despite the fact that we are seeing Accutane prescriptions within the data base. The numbers were small and in more recent years they dropped down to zero and for those reasons I will not be showing you those data.

In Florida there were no restrictions. In Michigan there were no restrictions until July 1, 1988 and then prior approval was required. In Minnesota there were no restrictions and in the two clients there were no restrictions.

(Slide)

We looked at three general groups of patients, males of all ages, females of all ages and females of reproductive age. What I will be showing you the results of is the third group, females of reproductive age.

(Slide)

The statistical analysis we performed is to look at the absolute rates of new users in each year, new users meaning people who had drug dispensed for the first time in one year and had not received the drug ever before that. We calculated 95 percent confidence intervals along with that. We then compared utilization rates in each year to the rates in the year before that, using 2 different methods, paired analyses and unpaired analyses.

Paired analyses are matched analyses. They basically assume total dependence. They assume that the same individuals were in the system one year as in the following year. In a Medicaid system that is not totally true. There is obviously a substantial turnover. A substantial minority of the patients in the system turn over from year to year.

The unpaired analyses assume total independence. They assume there is no commonality; none of the same people are present year to year. Obviously, in these data systems neither of the analysis is strictly correct. The reality is somewhere in between there. We did both of them in order to be able to get a span of what the results might be.

Due to pressures of time, I will not be able to actually show you the results of the analyses, unless there are questions, but I will mention them verbally.

(Slide)

This graph shows 1982-1989 new users of Accutane,

females, ages 12-45 in the 3 Medicaid states, Minnesota, Florida and Michigan. The horizontal axis is time. The vertical axis is use/10,000 women in that age range.

As you can see, in Florida the rates decreased in 1988. We do not have 1989 data yet. In Minnesota the rates peaked here and then decreased thereafter. They particularly went down in 1988, with little to no change in 1989. In Michigan we censored the data as of 1987 because of the prescribing restrictions that were put into place in 1988. The rates here virtually disappeared in 1989 after those prescribing restrictions but, obviously, that is artifactual.

(Slide)

Those same 3 curves are reproduced here on a different scale, along with the data from the 2 clients. As you can see, those 2 commercial clients have dramatically larger rates of use of Accutane than the Medicaid data sets, with very notable changes in usage. So in 1988 there was a small change. In 1989 there was a dramatic decrease in utilization. Some of the 1987-1988 changes and all of the 1988-1989 changes were statistically significant whichever way we did the analysis. We saw somewhat the same results in men as well, although a much less marked change in 1988 and 1989.

(Slide)

So our conclusions are that utilization of Accutane

by women of childbearing age decreased in 1988 and decreased dramatically more in 1989.

(Slide)

I will only briefly review the second study we did due to pressures of time. We were looking at outcomes following Accutane's exposures in pregnancy. The study subjects were Medicaid females of reproductive age who had a diagnosis of acne in the Medicaid files. We did not use the non-Medicaid plans because they did not have diagnosis information available.

The exposure groups were people exposed to Accutane, tetracycline, Retin-A, topical antibiotics or combinations of the above -- five different exposure groups. We compared the Accutane group to each of the other groups and to the combination of the other groups.

The outcomes we looked at were legal abortions, spontaneous abortions, unspecified abortions, live births and birth defects. Our conclusions are based on small numbers. There were not that many Accutane exposures in all of the three Medicaid data sets put together but, basically compared to the other patients who had been treated for acne, we did not see any obvious difference in the outcome of those exposed in utero to Accutane. I should add that we did get medical records to validate these outcomes. Thank you.

PRESENTATION BY ROBERT B. ARMSTRONG, M.D.

(Slide)

DR. ARMSTRONG: You have already heard a discussion of the controversial memo from 1988. When we were presented with this memorandum we divided our response into two parts. One part was an analysis of the factual data. The second part was a set of actions.

The quick summary of our analysis of the factual data was that there were not very much data presented, rather, there were models that projected estimates. On this basis, we did not believe that there was substantial objective evidence to support the claims that were being proposed. Indeed, at the time this memorandum was presented to the Advisory Committee, the authors were revising their estimates downward substantially, although, again, they did not provide objective data to indicate the basis for the numbers that they had generated.

So whereas we did not accept the mathematical analysis, we did institute a number of actions which were designed to promote the goal that I have already enunciated for you of preventing pregnancy.

(Slide)

You have the revised package insert in front of you and it has already been discussed so I will not dwell on it.

We then launched what I believe is the most extensive educational campaign ever produced for a prescrip-

tion drug. There are two main components of this that I would like to focus our attention on this morning.

The first is the pregnancy prevention program. There are a number of different elements to this but I would like to highlight two as being especially significant.

First, we were concerned that there would be patients who needed referral to another physician for contraceptive counseling and that these patients might not have the financial ability to obtain this consultation. Consequently, we made an unrestricted offer to assume the cost of this patient being referred for contraceptive counseling and a serum pregnancy test.

The second component of this that I would like to highlight is the detailed consent form. This form went through a great deal of detail. They are available to you if you wish to refer to them but there is an important part of this consent that I would like to highlight, and that is that the patient retained a copy of the consent form. This served two purposes. The first purpose was to remind the patient of her commitment to take the measures necessary to avoid pregnancy. The second was as a source of information that she could use for future reference. I will speak a little bit about the packaging that was changed.

(Slide)

Two months after the introduction of the pregnancy

prevention program, we instituted a series of surveys at two-monthly intervals looking at dermatologists and primary care physicians who had prescribed Accutane. We went to these physicians and asked them how many of their patients they had evaluated using different components from the pregnancy prevention kit.

As you can see from the most recent of these surveys, the one that was completed in March of 1990, the use of this program has remained high, even though it is 18 months after it was first introduced. In fact, the only component of this program that was not being used by the majority of patients is the referral for contraceptive counseling.

The reason that physicians most commonly gave for not taking advantage of the program was that they believed they were personally able to provide the appropriate counseling to the patient. The second most common reason was that the patient was already on an effective form of contraception and, therefore, a consultation would be redundant.

You will note that in this particular period 89 percent of the individuals were evaluated using a consent form that was provided by Roche. We do know that some physicians preferred to provide their own consent form.

(Slide)

What are the results of using this program? One

indication of its success is that as we did the survey we found that a substantial proportion of patients (22 percent) at the time this advertisement was prepared were not being given prescriptions because of the evaluation with the program.

(Slide)

This is the program that we have been running as advertising but I can tell you that the most recent number over this 18-month period is that 19 percent of patients were not prescribed the drug because of evaluation with the kit.

The second main point of this program had to do with the blister-pack. This incorporated extensive product information, including warnings and line drawings of the types of malformations that might be incurred, as well as verbal text that described as simply as possible the kinds of defects that could be seen and some that could not be seen. The purpose, clearly, was to reinforce the importance of avoiding pregnancy.

(Slide)

But there is another way in which this packaging was different from others. That is, each package includes an enrollment form that invites women of childbearing potential -- actually, women of any type -- to enroll in a study being coordinated by the Slone Epidemiology Unit.

(Slide)

I would now like to introduce Dr. Allen Mitchell, who is the associate director of the Slone Epidemiology Unit, to make a presentation on the results of that study to date.

PRESENTATION BY ALLEN A. MITCHELL, M.D.

DR. MITCHELL: Thank you, Dr. Armstrong. Good morning. In the little time that we have this morning I would like to present to you both an overview and some preliminary results and findings from the survey that we have been conducting at the request of Roche. I want to emphasize that our focus is exclusively on the time period beginning with January 1, 1989, which includes the beginning, essentially, of the pregnancy prevention program and what we are looking at this morning is physician and patient behavior subsequent to the introduction of the pregnancy prevention program.

(Slide)

The objectives of the survey were to determine primarily the rate of pregnancy among women who use Accutane and to also determine the important issues, such as the awareness of the teratogenic risks, their history of prior acne therapy, the pregnancy outcome among women who do become pregnant, the risk factors for the occurrence of pregnancy in that setting and the impact of the intensive survey that we designed on compliance with prescribing guidelines.

(Slide)

The survey design and conduct has been reviewed quite rigorously by an independent advisory committee to our unit, which is chaired by Paul Stoli, who is here today as an observer, and also includes Drs. Catz, Decker, McCoy, Melski, Pochi, Stern, Cordero, who is an observer, and technical advisers from Hoffmann-La Roche (names phonetic).

(Slide)

A consideration that should be borne in mind is that the survey monitors physician and patient compliance with the Roche pregnancy prevention program.

(Slide)

Because physician and patient compliance with the pregnancy prevention program is voluntary, survey participation is necessarily voluntary as well.

(Slide)

Because survey participation is voluntary, the population surveyed may not be representative of all women who use Accutane. In order to resolve some of that issue, we are trying to maximize enrollment and, at the same time, to assess the representativeness of the survey population.

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It is important to recognize that because of the urgency of implementing the pregnancy prevention program, and, therefore the survey, we did not have the usual luxury, I suppose, of a pilot study which is something that any

epidemiologic study would like to have. What you are then going to see is 15 months of experience that is somewhat on the job.

The outline of the survey components includes voluntary enrollment, as I have mentioned, and enrollment may occur by the physician or the medication package. We follow each patient for 6 months after discontinuation of Accutane for a typical course, which is, therefore, 11 months. The purpose is to identify any pregnancies that occur within the 6 months following Accutane. We follow up women in the survey either by telephone or by mail. We will be assessing the completeness and the representativeness of the survey population.

(Slide)

The physician-generated approach involves a physician asking a patient to complete the enrollment form at the time of the Accutane prescription. The medication package itself contains an enrollment form which the patient can complete. This form is designed as much to look like a consumer rebate certificate as an enrollment for a medical survey in the hopes that it would attract women who might not be attracted for other reasons.

(Slide)

The survey design looks something like this. We have, as I mentioned, the 11-month focus (5-month Accutane

but not package-generated approach. The totals that you see in the slide following may vary slightly due to some missing responses and the introduction of new questions.

(Slide)

To consider the years of education among the interviewed women according to the enrollment method, overall we see that roughly 53 percent have 12-15 years; 31 percent, 16-plus years; and the distributions by the 2 methods are quite similar.

I would like to summarize in anticipation some of the other slides with respect to the physician-generated versus medication package-generated breakdowns. In fact, the two groups of women are quite similar, as you will see, in their characteristics with respect to age, education, pregnancy risk and birth control methods. They do differ in the way their acne has been treated and in their compliance with the pregnancy prevention program -- something we think is quite an asset to the survey.

(Slide)

Prescriber specialty -- overall, 93 percent are from the dermatologists in the survey; 98 percent from the doctor-generated and 90 percent from the medication package-generated approach.

(Slide)

And the number of years of acne among interviewed

treatment and 6-month follow up). The enrollment was available through the physician-generated approach, beginning in January of 1989. As mentioned, the new medication package only contained the enrollment forms beginning with May of 1989. What I will not have time to discuss at length this morning is that as of about a month ago we, together with Roche, we have instituted a pharmacy project which is an effort directed at every practicing pharmacist in the United States to encourage women to enroll in the survey.

Upon enrollment, women are provided a payment of $10 which is sent to them within 48 hours of enrollment, and they are randomized to either the telephone arm or the mail arm -- maybe postal would be a better term, the postal arm of the survey.

The telephone arm involves 5000 women a year based on sample size considerations and involves a telephone call shortly after the prescription, within the first month essentially; another telephone roughly in the middle of the course of Accutane; and a final telephone follow up to identify the occurrence of pregnancy. The advantage, of course, in the telephone survey is that we are identifying information prospectively and we are avoiding the very substantial risks of recall bias if we only obtain information at this point.

There are two disadvantages. One is an obvious

logistic disadvantage if we are talking about tens of thousands of women to be followed in a year but, more importantly, we recognize that the telephone calls at the early part of therapy are in themselves an intervention and it is, therefore, important to try to get some understanding of what the experience would be in the survey population that is not contacted during the period of therapy.

For that reason, the mail arm, which consists of the remaining women, has one contact after the termination of therapy, which is a location mechanism, and then a final mail follow up equivalent to the telephone follow up at 11 months.

What I would like to point out is that we do not yet have information from the mail follow up. Thousands of those are being sent out over these few weeks and we hope to have that information in the next few months.

What I will be reviewing now is our experience with enrollments; the characteristics of the enrolled women and the experience to date, meaning the last quarter through March 31, with the telephone arm enrollment.

(Slide)

First let's look at the enrollment. This figure presents a quarter by quarter display of the enrollments, remembering that January, 1989 is when the survey began. The cross-hatch bars represent doctor-generated enrollments; the solid bars represent medication package enrollments.

Needless to say, in the first quarter they were all doctor generated. With introduction in May of 1989 of the medication package approach, we began to see the medication package forms having an impact. In the last three quarters, representing solid nine months, we have seen the full impact of the medication package option.

This allows us to reasonably project that we are likely to have approximately 40,000 enrollments a year. We suspect, and we certainly hope, that this will increase in the following quarters as a result of the pharmacy project. We find it hard to imagine that it would decrease for that reason.

(Slide)

Based on what we consider to be an unstable estimate of Accutane use, the PDS data, we project that our current enrollment rate, and I think it is important to stress that our current enrollment rate is 53 percent with the 90 percent confidence intervals derived from the PDS data, is 43-69 percent. It is also noteworthy that this enrollment rate appears to be the same whether we look at women of all ages or restrict our enrollment considerations to women in the childbearing 15-44 years.

Now let's briefly consider some of the characteristics of the enrolled women. If we look at enrollment by age, we find that the age categories overall are consistent with

what has been described for the use of Accutane and it is also noteworthy that the proportions of women by age are quite similar whether they are enrolled by the physician or the package mechanism. I think it is worth pointing out that the state by state breakdown is also quite similar to the sales figures provided to us by Roche.

(Slide)

What is the fate of the enrolled women? There were 32,000-plus people who attempted to enroll, of whom 760 were excluded. As of March 31, the current enrollment was roughly 31,500. They distribute into 24,000-plus into the mail arm and 7300 who had been assigned to the telephone arm.

(Slide)

Now let's consider the first telephone follow up which we call T-1. This is the information that we obtained from women immediately following their encounter with the physician who prescribed Accutane. Remember, this is a random sample of the survey population. It is conducted within 1 month of enrollment.

(Slide)

And let's consider some of the characteristics in compliance, bearing in mind that the first telephone interviews here involve 5361 women, completed and gone through quality control as of March 31. I think the distributions clearly reflect the early availability of the doctor-generated

women -- again it is worth noting that roughly two-thirds of the women report having had acne for six or more years.

(Slide)

Although this has been a difficult question, we asked women to describe the presence of cysts and we modified this question to try to get a better handle on this, working with our advisory committee. This refers to information collected over the last 4 months. What we find here is that 40 percent of women report having no cysts and 60 percent report having 1 or more cysts at any one time.

(Slide)

We also asked about antibiotic treatments for acne and what we found is that 78 percent report having received tetracycline; 57 percent erythro; 51 percent Minocin and other oral antibiotics.

(Slide)

We also derived the number of antibiotics used for acne prior to Accutane. What you see here is that roughly 70 percent of women report having received 2 or more antibiotics prior to their receipt of Accutane.

What I would like to do now is consider what women were told by their physician and what behaviors occurred at the onset of Accutane treatment.

(Slide)

We asked, "Did your doctor discuss the importance

of any of the following before prescribing Accutane?" What we found is that for most issues the majority of women received instruction but it was, of course, variable. Again you can see that the pattern persists that the doctor-generated forms tend to be more compliant than the medication package-generated forms.

(Slide)

One of the least discussed guidelines appears to be monthly pregnancy tests. Over 50 percent of women reported that their physicians did not discuss with them the need for monthly pregnancy testing.

(Slide)

On the other hand, one of the most important instructions that underlies the pregnancy prevention plan is the instruction to avoid pregnancy. Here we found that, irrespective of medication package- or physician-generated approach, the overwhelming majority, close to 100 percent, did report that they had been instructed to avoid pregnancy.

(Slide)

We also considered the number of women who reported having a pregnancy test before starting Accutane, according to a variety of options -- serum pregnancy, urine pregnancy tests and so forth. This was apparently a disturbing finding, 40 percent of women interviewed reported having no pregnancy test. One of the questions that came to mind was

could it be related to a woman's risk of becoming pregnant. We looked at pregnancy risk categories but we did not find that there was any real meaningful increase among women who were particularly at risk.

Then we wondered if, in fact, it was a flaw in the way the survey was asking the question. We were asking women if they had a serum pregnancy test. Is it possible that doctors were doing serum pregnancy testing by not communicating that fact to the women?

(Slide)

In the last 10 days, therefore, we conducted a survey on top of the survey in which we called the offices of doctors whose patients reported to us not having had a pregnancy test prior to starting Accutane. We indicated who we were and we told the physicians that we were doing a survey, as part of the survey, to identify the blood tests that were performed in female patients who were prescribed Accutane. Our intended survey was 100. There were 10 refusals and 4 calls are still pending as of last week. So we had 86 calls that were completed. Of interest, the majority of the information came from the nurse or the office manager.

(Slide)

The offices volunteering their pregnancy testing is obtained routinely amounted to roughly half of those that

were contacted. Roughly another 20 percent indicated that they did pregnancy testing selectively. We did not identify that we were interested in pregnancy testing in these questions. That selective category represents a broad range, as you might guess. Some physicians' nurses said they do it on all women of childbearing age. Others said they do it if they think a woman is at risk. So it appears that roughly three-quarters of women reporting no pregnancy test were likely, indeed, to have had one.

(Slide)

We then wanted to examine contraceptive practices. In order to do that, we ought to first look at who was at risk for pregnancy in the survey population. Overall, there were 36 percent of the surveyed women (similar in both groups) who reported not being sexually active and 60 percent who reported that they were sexually active. It is, of course, important then to consider what the birth control practices are among this group of women who report being sexually active.

(Slide)

This slide refers to the use of contraception among sexually active women according to their enrollment method. What we find is that 99 percent of the women who report being sexually active report using contraception. Incidentally, this is a typo. This should be 1.2 and I apologize for that.

It is also important to note that these 34 women in this category are identified as program failures. These are women to whom we gave warning --we discussed this last year as well, I believe -- and if they give us permission we call their physician as well.

(Slide)

We examined the birth control methods among women currently using birth control. What we found is that overall 53 percent of the women in the survey report using oral contraception. This is much higher oral contraceptive use than the general population of the same age would suggest. As you might expect, when we stratify this by age the younger women are much more likely -- in fact, it turns out to be about 83 percent -- to use oral contraceptives. The older women are much more likely to use methods of sterility -- tubal ligation and vasectomy, as well as about 37 percent of those older women reporting use of OCs.

(Slide)

What I have provided is the information we obtained at the first telephone follow up. That identifies what women were told and what they were doing at the outset of therapy. But what is the carryover?

The second telephone interview provides us an opportunity to consider the retention of information by the women and also the persistence or lack of persistence of

their compliance.

(Slide)

Briefly, one of the questions we asked was, "What do you remember as the most important instruction to follow while taking Accutane?" And 85 percent of women continue to report that avoiding pregnancy is the most important instruction to follow.

(Slide)

Importantly, of course, as well is sexual activity and what protections are being taken. When we looked at the sexual activity reported among women interviewed both at the first and the second telephone interview, we found that of 1043 women reporting to be sexually active at T-1, 94 percent continued to be sexually active at T-2 and 6 percent had ceased. On the other hand, there were 18 percent of the women who initially were not sexually active who had become sexually active. Clearly, one is concerned about their risk and their use of contraception.

(Slide)

We, therefore, looked at use of contraception among women who were sexually active at the T-2 interview. What we found was that 99 percent of the women who were persistently sexually active (almost 100 percent), continued to use some form of contraception. Interestingly, among the women who had since become sexually active, 98.4 percent report as well

that they are using some form of contraception.

(Slide)

Finally, let us consider the pregnancy rate, as distinct from the term pregnancy exposure, of the women in the telephone arm of the survey. This pregnancy rate estimate uses the risk period as that period of time involving Accutane exposure only, in other words, while the women were on drug. We interviewed 5275 women who formed the basis of this analysis. We identified a total exposure of over 388,000 person days or 1065 person years. We have identified 3 pregnancies based on that denominator of exposure, for a pregnancy rate of 0.3/100 person years, 2.8/1000 person years.

I also erred in the information I provided most recently to the Committee. These are not data as of May 10, which was the date of preparation. These data, like all other data, are through March 31 of 1990.

But we also should consider a different pregnancy estimate. This is a rate estimate that includes the 30 days following discontinuation of Accutane because, strictly speaking, that is one of the prohibitions on the package insert.

(Slide)

When we do it that way, we increase the number of person days, of course, and increase the number of patient

years. We now pick up an additional 2 pregnancies in our numerator. Two of the 5 pregnancies we have identified through the telephone arm were women who became pregnant following discontinuation of Accutane. That translates to a rate of 0.5/100 person years or 4.5/1000 person years. This is the rate which we feel is the appropriate one to serve as comparisons.

(Slide)

Where do we stand? Clearly, we do not feel the survey has provided the information yet that we promised to provide, although we are on schedule. In May of 1990, we feel that the survey is working from a logistics standpoint. We have accomplished the objectives that we could not guarantee accomplishing up front.

The information provided to date, we believe, is informative, although at this moment it refers only to the telephone survey. We have yet to accomplish the task of assessing the representativeness, which is work that is under way at the present time.

(Slide)

In fact, our work in progress includes assessing the impact of the pharmacy project on enrollment; in the telephone survey, obtaining more stable estimates as the numbers increase of the pregnancy rate. In the mail survey we, of course, want to estimate the pregnancy rate. We want

to evaluate the impact of the telephone intervention relative to the mail follow up because, as you may remember from previous hearings, if it were to prove to be the case that the telephone survey was a more effective intervention, then that would be a mechanism applied to the entire survey population in the future. If the mail survey were to provide equivalent pregnancy rates, that could be provided more cost effectively.

Finally, we wish to assess the representativeness of the survey population. That work, using some prepaid data bases, will take place over the next few months.

I thank you for your time and I will be happy to answer questions at the appropriate time.

PRESENTATION BY ROBERT B. ARMSTRONG, M.D.

DR. ARMSTRONG: Dr. Mitchell has brought us up to the last few weeks. So we are contemporaneous now. Within the last couple of weeks you, as well as we, have received a new memorandum from the epidemiology group at the FDA.

(Slide)

We would like to respond to that report by saying that our analysis of it, of which you have a detailed copy, albeit not very long ago -- we did not accept the contention or the claim that unreported birth defects continues to be a substantial problem.

(Slide)

I will divide the comments on that into several sections, beginning with the importance of having accurate data on which to make one's assessment. Since we are discussing now the denominator, the number of women at risk that have not had a birth defect reported, we need to have confidence in the numbers that are being projected.

I am going to select a few examples. Time does not permit me to go through all the examples that are specified in the analysis that has been sent to you. But there are a few examples that lead us not to have confidence in the methodology being applied.

First, in discussion of the usage of drug, the memorandum states that the NPA data base has 2000 computerized pharmacies. In fact, NPA tells us that they have 2500 computerized pharmacies and an additional 600 manual pharmacies. The memorandum maintains that the usage projections from NPA are under-reported because it does not include chain or discount pharmacies. In fact, this is also incorrect. NPA has a total of 53 percent of their sample in chain or discount pharmacies relative to 37 percent of the total pharmacy universe. So again the basis for making the claim that usage is underestimated is based on false premises.

The second point has to do with the under-reporting in women below the age of 23. The memo contends that in the PDS data system is under-reported because the age and sex of

the patient is not specified or recorded frequently and, therefore, the usage is probably under-estimated.

So we contacted PDS and found out how often the age and sex were not recorded to justify the term that it is non-quantitative but connotes a feeling of quantity. It turns out that it is actually 3 percent of their prescriptions that did not specify the age and sex of a patient, hardly enough, it seems to me, to justify the conclusion of probability.

(Slide)

The next part of the memorandum deals with Medicaid studies. Here we would start off by saying, as this group is quite well aware, that a number of those population characteristics that determine the success of contraceptive measures are not representative in the Medicaid population compared to the total population. For this reason, any results that are found in the Medicaid study would be difficult to project to the general population.

Of greater concern to us, however, is the apparent lack of documentation in this report. It is not indicated whether the patients who are identified as suspected pregnancy exposures, based on having filled a prescription and having a subsequent pregnancy-related code, actually took the drug. Or, if they did take the drug, took it at a time that would involve exposure of the fetus. So without this kind of information, we are not in a position to be able to meanir

fully interpret the data that are being presented to us.

Finally, the memorandum we were presented two years ago discussed five adverse birth outcomes. This study, two years later, indicates three adverse birth outcomes, one of which was a stillborn infant with a cord around the neck, without any indication that there was any relationship to Accutane. It did describe one case of a birth defect but, again, it is not clear whether this was an Accutane-exposed pregnancy and also it is not indicated whether the birth defect was of the type that is attributable to Accutane. So for these reasons, we find it impossible to make an adequate assessment of the claims that are being presented.

Finally, in terms of calculating relative risks, the control group that was used for comparing Accutane was the entire female population within Medicaid. Since that population would include women who had had hysterectomies, tubal ligations or who were postmenopausal, it clearly would have an influence on their relative risk for pregnancy-related outcomes. Dr. Strom presented earlier a case where the control group was acne patients treated with Accutane or other antibiotics, which we believe is an appropriate control group.

(Slide)

Finally, the bulk of the conclusions on estimates of exposure and under-reporting are not based on data but are

based on mathematical models. These models are done using assumptions from general populations in the literature and they make no allowance for the possibility that there would be greater motivation of Accutane patients when they were educated to understand that there was a very high risk of birth defects resulting from pregnancy exposure. As you well know, motivation is a key component of successful contraceptive practice and we think it is unrealistic to think that there is absolutely no effect of the educational campaign, not only on the patients but also on the physician selection of patients as being appropriate for therapy.

Finally, we would like to have some idea of how the selection of different numbers for the different variables might alter the outcome. By doing a sensitivity analysis, we would be able to judge the best case/worst case scenario as an indicator of how good the model was. Unfortunately, there is no sensitivity analysis presented in the memorandum and the equation is also not provided. So we are not able to do an independent assessment to find out how much reliance one should place on these calculations.

(Slide)

Finally, the memorandum concludes that the pregnancy prevention program is a failure. I would like to ask what are the data for making that conclusion.

The first thing that is discussed has to do with

usage and I have already given you some reasons why we do not have confidence in their argument. But I would also like to maintain that the important issue here is not how many women use Accutane but how many women use Accutane while they are pregnant, which is really the crux of the prevention of birth defects issue.

In fact, the only quantitative data that are presented in the memorandum come from the Harvard Community Health Plan. These data are obtained over a two-year period and are divided to compare pre- and post-intervention outcomes.

Here I would like to point out that the time period that was selected to divide these 2 periods was May, 1988, whereas, in fact, the first element of this program was not introduced until 4 months later and the final element was not introduced until 12 months later. It seems only fair to make one's judgment based on the time that the program had at least been implemented.

Secondly, this Community Health Plan data involves less than 200 patients over a 2-year period and, therefore, are less in sample size than the 31,000 patients who have already been enrolled under the Slone Epidemiology Unit.

For these reasons, we have reservations about how much confidence we can have and how to generalize the results from this study.

(Slide)

Finally, we think that the conclusion that women of childbearing potential should be excluded from the possibility of fetal exposure, presumably by denying them access to Accutane, is an unwarranted and drastic action. It seems to me that physicians and patients need to be informed of all of the issues that we have discussed and that we have been at great pains to educate them about, and those kinds of activities have been reflected as successful in the results that we have so far of the Slone epidemiology survey. Clearly, we need to have questions about the quality of the data in the Slone epidemiology survey answered but the mechanism of testing the quality of those data is already being tested.

(Slide)

Having rejected the conclusions of this memorandum, I do not mean to suggest that we are not prepared to take additional measures to the ones that we have already taken. Indeed, through the Slone survey we have identified that there is a need for a new educational campaign to reinforce the importance of doing a pretreatment serum pregnancy test and also to make sure that the test report is negative before treatment is begun.

In connection with that, we will have a new educational campaign to reinforce the importance of starting

Accutane on the second or third day of the next menstrual period to avoid the possibility of a false-negative test in the outcome that we presented earlier.

Finally, there is so much information on the packaging material that we thought it would be useful to provide a bulleted format that would highlight the particular importance of a pretreatment pregnancy test, waiting until the second or third day of the menstrual cycle and use of an effective contraceptive. We thought that the easiest way to achieve that would be to provide a sleeve that would wrap around the current packaging and highlight these warnings so that they would be brought specifically to the patient's attention and have detailed information available for further study. We will propose this to the Agency and attempt to implement it as soon as it can be arranged.

We talked earlier about patient self-treatment. So we wish to establish a means of encouraging patients to return unused Accutane that they have not used in the course of their treatment. The details of this have to be worked out. Presumably, they will present some logistical challenges but we think that the ability to, in a sense, recall the unused medication will reduce the possibility of patients taking the drug subsequently without supervision of their physicians.

We also propose to meet with representatives of

organized medicine and organized pharmacy to explore the possibility that prescription forms might be developed that would reinforce the importance of the negative pregnancy test, avoiding pregnancy and some of the other warnings that have been provided in other formats. Clearly, there will be about state laws in trying to implement any of these proposals.

(Slide)

Now I would like to ask for help from the Committee, if I could. One of the ways that we think might increase the number of pre-therapy pregnancy tests that would be done would be to consider the possibility of using a urine test done as an office procedure. We would like to have your advice as to whether this would be a desirable recommendation for implementation or whether the serum pregnancy test should be continued.

Second, we would like to ask the Committee to suggest ways that might maximize the effectiveness of contraception for women while taking Accutane.

(Slide)

I do not mean to suggest that this is the last of the things that we would be prepared to do. Indeed, our history with this drug has been that we have sought to learn from our experience ways in which we could reinforce the messages in a way that would be productive. We intend to

continue, not only to implement with full vigor the program that has been implemented so far, but we are also prepared to take additional steps as experience would indicate to be appropriate.

(Slide)

So in conclusion, we have unprecedented programs that we have introduced to support the proper use of this drug and we continue to support those fully. We now have the prospect of getting meaningful data from the Slone survey which will be helpful to us as we consider what additional steps might be important to take in the future.

Finally, I would like to conclude by welcoming any contributions that the Committee members would care to offer that would help us to promote the goal of avoiding pregnancies and, thereby, preventing birth defects. Thank you.

DR. SCHROETER: Thank you. We have finally a review of data by a representative of the FDA's Office of Epidemiology and Biostatistics.

PRESENTATION BY DAVID GRAHAM, M.D.

DR. GRAHAM: Good morning. My name is David Graham and I am a medical officer with the FDA and section chief in epidemiology. I hope that members of both Committees have had time to read the report I prepared for the Division of Anti-Infective Drug Products.

Today I will highlight some of the important

features from that report but time will not permit an in-depth presentation of many areas covered by it. I have passed out to members of the Committee copies of several overheads which were made up late last week and which were not included in our original report. These will be used later to address several questions raised by the sponsor.

(Slide)

In April, 1988 I presented data, developed by FDA's Office of Epidemiology, on maternal exposure to Accutane. We described the epidemiology of cystic acne and used existing national survey data, as well as the published literature, to estimate the incidence of severe cystic acne unresponsive to other therapies in women.

We showed that Accutane was used extensively in women of childbearing age, with over 40 percent of all Accutane use in women 15-44. We concluded that Accutane was used outside of its labeled indication over 90 percent of the time in women and further showed that pregnancy exposure to Accutane during the first trimester of pregnancy might be a frequent occurrence.

Following this meeting, FDA and the sponsor embarked on an unprecedented intervention program. The goals of this program were publicly stated before both Committees present here today, and are summarized on this slide.

The goals are the elimination of pregnancy exposure

to Accutane and reduction in level of use of Accutane in women to a level consistent with the labeled indication and the incidence of disease. My presentation today will focus on evaluating the status of Accutane with respect to these goals covering the two-year period since I last spoke before this Committee.

(Slide)

Before proceeding, I want to re-describe for the Committee how our Office arrived at its estimate for the incidence of severe cystic acne in women aged 15-44. We used the age 15-44 as a surrogate for the reproductive age range. We began with the prevalence of cystic acne found in the National Health and Nutrition Examination Survey (NHANES). This study was designed and carried out by the National Center for Health Statistics.

In that study, 20,000 people from across the United States were selected by a carefully designed random sampling technique. They were examined by 200 specially trained dermatologists who followed a tested protocol.

The study found that cystic acne was 5.5 times more common in men than in women. The prevalence of disease of all degrees of severity, not just the severe disease but all degrees of severity, active as well as inactive, was 0.6/1000 or, as shown on this slide, 6/10,000. That is 6/10,000 women aged 1-74 years of age.

This prevalence was multiplied by the population size of females in that age range which, in 1988, was 116 million. This gives you sort of a sense of what the prevalent pool might be for cystic acne if we did not have Accutane present today.

From the published literature, a mean duration of cystic acne of 10 years, more or less, was obtained. This is substantiated by the data from the Slone group where 2/3 of patients have durations of acne greater than 6 years.

Also from the literature we estimated conservatively that 50 percent of all cystic acne would qualify as severe according to the definition of severe disease used in the premarketing studies. From the Slone study data that we have seen, we noted that 16 percent of the patients enrolled in the study had 5 or more cysts. The definition of severe upon which Accutane was approved and on which the premarketing trials were done required that patients have 10 active cystic lesions. So requiring that severe was only 50 percent is a very conservative estimate in favor of the sponsor's view.

We then used the epidemiologic relationship of prevalence equalling incidence times duration to solve the equation for incidence. We arrived at a number of fewer than 4000 cases per year in women 15-44.

(Slide)

With this information as background, I will now

present data on Accutane usage in women. This slide shows the number of prescriptions for Accutane as estimated by the National Prescription Audit for years 1982-1989.

In 1989 there were 726,000 prescriptions for Accutane, representing a 19 percent decrease from the previous year. When analyzed by year for trends in prescribing, a no downward trend was noted.

(Slide)

This slide shows Accutane prescription data from the National Prescription Audit by quarter of marketing from 1982-1989. The drug came out in September, 1982 and that is just about the start of the fourth quarter. So it goes from there up until the end of the first quarter, the end of March, 1990.

Generally, over this period of time there were more or less 200,000 prescriptions for Accutane per quarter. Apparent from these data is the seasonality of Accutane prescribing, with nadirs occurring generally during each summer quarter, which is the third quarter.

The number of prescriptions fell in the summer quarter following the April, 1988 advisory meeting according to what one might expect to be the typical summer nadir based on previous experience. However, the typical increase in prescriptions which is seen in the fall and winter quarters did not occur following the advisory meeting.

The following summer, the third quarter of 1989, saw a further drop in prescribing, with a return back to previous levels in the fourth quarter of 1989 and the first quarter of 1990.

The prescribing of Accutane in the past year and a half has demonstrated the same cyclic form and shape as prescribing of Accutane since it came on the market. The only difference is that it is at a somewhat lower level. Because the levels of prescribing for Accutane during quarter 4 of 1988 and 1 of 1989 are about the same as 4 and 1 of 1989-1990, we believe that a new equilibrium in prescribing for Accutane has been established. In every single year of marketing, proportion of Accutane used by women of child-bearing age has ranged from about 40-45 percent of all use. The nearly 1:1 ratio of use for men and women stands in sharp contrast to the sex ratio of disease where men outnumber women by a ratio of 5.5:1.

(Slide)

This slide shows data obtained by the sponsor from Prescription Data Services, representing estimates of the number of women age 12-44 newly treated with Accutane by year. Between 1982-1989, the system estimates that 605,000 women in this age range were treated with Accutane. This is about 1 percent of all women in this age group. The level of new starts in 1989 was virtually identical to that in 1988.

The sponsor has applied a regression line from data in 1983 down through the data in 1989 and found a "statistically significant" downward slope. This observation is driven by the high number of prescriptions in 1983. Such a trend line diverts our attention away from what happened in 1988 and 1989, which is really what we are interested in.

Even if such a regression line did apply to these data and did correctly predict future prescribing, it would take until about year 2020 for prescribing of Accutane in women to come anywhere near what the estimated incidence of the disease is. However, these data, we believe, suggest that a linear model is not appropriate, especially because of the flattening of prescriptions for 2 consecutive years at the end.

(Slide)

This slide compares prescribing of Accutane on a quarter by quarter basis for the years 1988 and 1989. Prescribing was virtually identical quarter by quarter for both years. In this section we have shown that Accutane use by women of childbearing age has not changed in 1989 compared to 1988. The level of use in women exceeds the estimated incidence of disease and the labeled indication for the drug by more than 15-fold. This means that over 90 percent of women treated with Accutane last year did not have severe recalcitrant cystic acne. Nonetheless, these patients did

receive Accutane and were subjected to the risks of pregnancy exposure, birth defects and abortion which are associated with such exposures.

I now want to shift to another topic and update the Committee on our work using the Michigan Medicaid to study Accutane use and pregnancy exposure. These data shed light on the nature of Accutane pregnancy exposure and its ramifications. Our previous data on this were requested by both California and Michigan and were used by both in arriving to their decision to remove Accutane from the general formularies of their Medicaid programs.

From 1982-1988, 1122 women, aged 15-44, were treated with Accutane in Michigan Medicaid. For future reference, this group formed our Accutane treatment cohort. We compared this group to the population of 278,000 women aged 15-44 in Michigan Medicaid who did not receive Accutane. This group was the untreated cohort.

Each patient in Michigan Medicaid has a separate record of billable Medicaid transactions. This covers physician visits, prescription services, hospitalizations and outpatient procedures. This record, referred to as a medical profile, lists in sequential calendar order all reimbursable medical transactions. The computerized profiles of the 1122 women in our Accutane treatment cohort were reviewed to identify women with suspected pregnancy exposure.

(Slide)

This slide demonstrates the approach we used. It has been described in several previous studies of other drugs published in the obstetrical literature. If an Accutane prescription extended to within 270-180 days prior to a delivery or to within 120 days of an abortion outcome, this woman was classified as having a suspected early pregnancy exposure to Accutane. In our cohort of 1122 women, 65 women (5.8 percent of the total) were found to have suspected early pregnancy exposure to Accutane.

The next two slides present in annotated fashion the information from profiles on two women from our study. They are intended to give the Committee a sense of the data available and how our classification algorithm works.

(Slide)

This woman entered the Medicaid system about 5 years before she received her first Accutane prescription. Her first diagnosis and therapy for a skin condition was 3 years before receiving Accutane. She received some topical therapies but no systemic antibiotics. At 281 days prior to delivery she began Accutane, receiving 3 consecutive monthly prescriptions throughout the entire first trimester of pregnancy. There was no billing for a pregnancy test and no evidence of prescription contraceptives.

At 198 days prior to delivery there is a code for

spontaneous abortion in this woman's profile. This was apparently a rule out diagnosis because at 120 days before delivery there is a diagnosis of fetal abnormality in the woman's record. The woman delivered and at that time the medical records show that the child was normal, except for a caput hematoma, which is a routine finding with vaginal delivery.

(Slide)

The second slide shows the profile of another woman from our study. She entered the Medicaid system about 3 years prior to the beginning of this slide. I have not shown that because there was not enough space. Her first diagnosis and treatment for acne occurred about 1.5 years before her first Accutane prescription. All told, she received about 3 months of systemic antibiotics. However, there were large gaps between these prescriptions. They were not administered consecutively as the literature recommends. Also the dosages of antibiotics were not sufficiently high for cystic acne if, indeed, that is what this woman had.

She began Accutane therapy 276 days before delivery. She received several different prescriptions at regular intervals throughout the first trimester. The woman began prenatal care at 93 days before delivery. She had poly-hydramnios at delivery. The baby was born with hydrocephalus and CNS abnormalities and died at 8 days of age.

These two slides emphasize that Accutane exposure in the first trimester does not cause birth defects in 100 percent of cases, as the current labeling implies. Current data suggest that the risks of birth defects may be as high as 25 percent but may be lower.

In a critique of our work, the sponsor stated that data from Medicaid should not be believed because we have not yet documented that the women prescribed Accutane actually ingested it. For reasons of protecting patient identity and confidentiality, Michigan Medicaid as declined to permit us to interview these women. We believe the data are useful and reliable, however, because over 70 percent of women in the Accutane exposure cohort received more than 1 prescription. This suggests to us that the women not only filled their prescriptions for Accutane but also took the drug. The prescription sizes and the time interval between prescriptions as seen in this profile and the profile before it seem to bear this out as well.

(Slide)

This busy slide summarizes the distribution of suspected first trimester pregnancy exposures to Accutane in 65 women. Of note, the level of exposure was fairly consistent from year to year. Also abortion was the outcome in 76 percent of cases. In 60 percent the outcome was induced abortion. This compares with the background rate in the

Medicaid population for induced abortion of about 30 percent. For spontaneous abortions were recorded in these women. This is lower than would be expected based on the data by Dr. Lammer, which was presented before this Committee last year.

Dr. Franz Rosa, from our Office, has studied this particular diagnosis in detail. He has shown that data from Medicaid cannot be used to reliably study spontaneous abortion because the system fails to capture the majority of events. This occurs because women in Medicaid typically do not seek prenatal care during the first trimester when most spontaneous abortions occur.

Twenty-four percent of women with suspected Accutane exposure in the first trimester deliver. There were deliveries in every year except 1983. Of interest and concern, we found that 21 of these 65 women (32 percent of the total) were probably already pregnant when they received their first prescription for Accutane.

(Slide)

We reviewed the maternal profiles of all 16 deliveries and have, thus far, obtained infant profiles on 5 cases and some medical records on 10 cases. Based on these preliminary data, 12 births were normal; 1 child was stillborn with the umbilical cord wrapped around its neck; 1 child, whose mother's profile you have just seen, had a severe birth defect and died 8 days later; 2 are uncertain. One died

perinatally but this child was premature and we have not yet learned if the death was due to prematurity or some other cause. The other child has an ICD9 code in the mother's profile for fetal damage due to drug. We are awaiting this child's profile and medical records.

We still have much work to do in trying to collect as much information as possible on the deliveries. We hope to eventually obtain medical records for all deliveries and the offspring.

To validate the deliveries, several things have been done. First, a previous study for another drug, conducted by our Office, found that 100 percent of patients with inpatient delivery codes in their profiles had an actually delivery. This was done for 63 women with inpatient delivery codes. In our own group of 16 patients, all 16 have inpatient delivery codes and all but 1 have multiple recorded prenatal or postpartum outpatient visits, as well as prescriptions for prenatal vitamins and Parlodel for postpartum lactation suppression in many.

This provides internal verification that the pregnancy and the delivery were real. We are also cross-referencing our cases with a procedure code file, which should give us added certainty and security in this conclusion. The abortion accounts are also believed to be valid because ongoing auditing by Medicaid to detect and punish fraudulent

billing or procedures occurs. Half of our abortion cases also show prescriptions for oral antibiotics and ergot derivatives on the same day as the abortion code, suggesting that the procedures were, in fact, carried out. We are in the process of running our case material across a separate file of reimbursable procedure codes as a means of validating the cases without ergot or antibiotic prescriptions.

(Slide)

We were interested in the pregnancy outcomes of women with suspected first trimester exposure to Accutane. To study this question in more detail, we calculated the incidence densities for pregnancy, abortion and delivery among the Accutane-treated cohort and the population cohort not treated with Accutane.

These crude rates per 1000 women years were derived and are shown on this slide. Relative risks were calculated as incidence density ratios according the method of Guess et al. and Rothman and Boyce. The pregnancy rates in the 2 groups were similar. The relative risk was 1.1. This suggests little difference in contraceptive practice or efficacy for the women in the Medicaid system.

Medicaid uses a number of different ICD9 codes to describe abortion, including legal induced, spontaneous and not otherwise specified. We calculated relative risks for each of these codes and for all codes together. Abortion

events, especially induced abortion, showed elevated relative risks. We found a 2-fold increase in abortion among women treated with Accutane when compared to Medicaid women not treated with Accutane. The 95 percent confidence intervals are narrow and these results are highly statistically significant.

Delivery in the Accutane-treated population was half that of the general Medicaid population. These data were adjusted for age and race. Marital status and socio-economic status, which are also known to be potential confounders in abortion, are internally self-adjusted. Low income level and single parent status are pre-conditions for Medicaid eligibility.

To search for possible risk factors of pregnancy exposure to Accutane, we performed a nested case control study comparing the 65 women with suspected Accutane pregnancy exposure, our cases, to 99 women treated with Accutane but not experiencing pregnancy exposure, our controls. This control group was obtained by taking a 10 percent sample of the entire Accutane treated cohort of 1122 women.

We then excluded those women over the age of 44 or under the age of 15, as well as any women with an Accutane pregnancy exposure. Out of 112 women selected by a random sample, 99 were age 15-44 and had not had pregnancy exposure to Accutane.

(Slide)

Age and daily dose did not differ between the 2 groups, in our case group or our control group. The number of prescriptions were lower and the duration of therapy was shorter among women with pregnancy exposure. You can see that here. Both of these were statistically significant. This difference was explained entirely by the presence of the 21 women who, based on the timing of Accutane use with respect to pregnancy outcome, were probably already pregnant when they received their first prescription for Accutane. When these 21 women were removed from the group of 65, the differences between cases and controls disappeared.

(Slide)

We were unable to fully ascertain contraceptive practice because over-the-counter methods are not included in patient profiles. However, there appears to be less compliance with prescription forms of contraception among women who experienced pregnancy exposure compared to those who did not.

Pregnancy testing was rarely performed and few patients received adequate prior antibiotics. Among patients receiving any antibiotics, it was generally of a short duration and a low dose.

(Slide)

A number of criticisms were raised about the

unrepresentativeness of Medicaid populations. Medicaid populations are poorer, have lower education levels and higher proportions of women of minority groups than the general population. Patterns of health care utilization may also differ. Some have suggested that the quality of health care these patients received and the physicians who provide such care may be inferior to that available outside of Medicaid.

However, certain aspects of Accutane usage bear emphasizing. The annual prevalence of Accutane use in women nationally is about 1.2/1000 women. In Michigan Medicaid the use level was about 1/1000 women per year.

The age distribution of women treated with Accutane in Michigan Medicaid is virtually superimposable on that from the Slone Accutane study, the results of which we just saw previously. It is also virtually identical to the distribution of ages for the group health cooperative HMO, data which we presented to this Committee last year.

The mean duration of Accutane prescriptions among women in Michigan Medicaid was 22.5 days. This was exactly the same as that for the nation as a whole, as estimated by IMS America and reported by the sponsor in their critique of our original report.

The proportion of women receiving only 1 prescription of Accutane in Medicaid was 28 percent. In the

Province of Saskatchewan, in Canada, with universal health insurance in a non-impoverished environment, 30 percent of patients had only 1 prescription. These data have been published in the Canadian Medical Association journal. In both Michigan Medicaid and Saskatchewan only about 19 percent of patients received 4 or 5 prescriptions for Accutane, which would correspond to the recommended treatment duration. These features suggest to us that Michigan Medicaid may not be as unrepresentative as alleged by some.

Two years ago we proposed a system that would have permitted an accurate counting of pregnancy exposure and birth defects with Accutane. The system was not adopted and today we still have only spontaneous reports of birth defects and pregnancy exposures to rely upon.

The sponsor says that the only pregnancy exposures and birth defects which have occurred are those reported to it. Our Office maintains that most cases go unreported. In the absence of a system permitting full enumeration and verification of pregnancy exposure and birth defects, we developed a model based on national data to estimate the magnitude of pregnancy exposure to Accutane.

This model was developed for heuristic purposes only, to give us an impression of what is most likely occurring. The actual numbers are far less important than is the insight which the model provides.

(Slide)

As we have conceptualized it, the total number of pregnancy exposures to Accutane is the result of the contribution of 3 separate components. Exposures can result from initiation of Accutane therapy in women who are already pregnant. Exposures can also occur among women who are sexually active but not practicing any contraception. Finally, exposures may be related to contraceptive failure itself.

(Slide)

We designed a model which incorporated data on the distribution of various pregnancy risks and contraceptive categories, as well as pregnancy rates associated with each of these categories. This was used to estimate the number of pregnancy exposures to Accutane which we believe probably occurred. The Committee has hard copies of the overheads I will be using.

(Transparency)

This overhead shows the formula we used to arrive at the estimate of pregnancy exposures. We summed overall pregnancy risk and contraceptive categories. The number of women treated with Accutane, 65,000 in 1989, was multiplied by 5/12 because the typical course of therapy is supposed to be 5 months and that is 5/12 of a year. This converts the number of patients into person years of exposure to Accutane.

This quantity was multiplied by the proportion of women in given contraceptive risk categories and by the associated pregnancy rates for those categories.

I have given an example for oral contraceptives. We have 65,000 women; 5/12 of a year; a 0.243 proportional prevalence in the population for OC as a method of contraception and a failure rate of 2.5 percent. That result leaves us with 165 pregnancy exposures due to pill failure alone.

For all methods, including no method, we summed this formula and then added a term to adjust for that proportion of women who were already pregnant when they started Accutane. We know that for the years 1982 up through 1988 that that proportion is about 1/3 of the pregnancy exposures, which meant that the total sum that we would get over all methods here would then be increased by an additional 1/3 due to exposure of women who were pregnant when they came to the doctor and got their first prescription for Accutane.

In our original report we used data provided in an overview article on contraception, by Dr. Mitchell, which appeared in the New England Journal of Medicine. The data which he used was the derived from the National Survey of Family Growth, which is sponsored by the National Center for Health Statistics. These data are shown in the next slide.

(Slide)

These rates were those which apply to U.S. women aged 15-44, obtained from the most recent previous National Survey. Given the sampling design of the survey, these data are the most representative data available to describe the situation in the United States.

(Slide)

Using our model, we estimate that between 1982-1988 there were about 16,000 pregnancy exposures to Accutane, affecting about 3 percent of women treated with the drug. The majority of these were aborted. There were perhaps 900 birth defects.

The sponsor claims that we intentionally picked the highest contraceptive failure rate in our model, resulting in an unfairly skewed picture. They have asked today for a sensitivity analysis.

The examples of the lower contraceptive failure rates cited by the sponsor in their critique of our report refer primarily to foreign studies, done as clinical trials within specific subpopulations, for example, married women aged 30-39. These data were not referenced to the total population of women 15-44. The data which we used was referenced to the entire U.S. population.

To explore the sponsor's concern further, we consulted with contraception experts at the Centers for Disease Control. They referred us to the work of Trussel and

Kost on contraceptive failure, published in 1987. Trussel is one of the most respected contraceptive demographers in the world and the work presented in his paper has come to be accepted as the most accurate and definitive data in the United States. His rates are those which are used in the reference work, Contraceptive Technology, which is the final authority in the field of family planning.

(Transparency)

Trussel and Kost performed a clinical review and analysis of the existing published literature on pregnancy with various methods of contraception. This overhead describes their findings. The first column shows the numbers that we used in our model. The next two columns are from Trussel and Kost's review. The column labeled "typical observed" refers to the real world, actual pregnancy rates observed in large population-based studies. The column labeled "lowest expected" represents the theoretical lowest pregnancy rate which would be observed if only perfect users of each method were studied.

As Trussel and Kost point out, this is never seen and the rates for "typical observed" are what are almost universally experienced. Please note that in each instance of our model the rate which we used was lower than the "typical observed" rate which Trussel and Kost say is what the most likely experience is in the population.

In their review, Trussel and Kost discuss the studies which produced the low rates for vasectomy, tubal ligation and no method, which we have in our model. If you compare tubal ligation, we have a rate that is much lower than the theoretical minimum; for vasectomy, much lower than the theoretical minimum; and for no method, much lower than the theoretical observed.

In their review discussing the sources for the data which Mitchell included in his paper and which we included in our review, they point out that each of these studies had serious design flaws and biased methods of accounting for person time which resulted in substantial under-calculation of the pregnancy rates with these methods.

To represent a more balanced and realistic view, we used the data from Trussel and Kost, as well as additional data provided by the Slone study on the distribution of contraceptive methods, to estimate pregnancy exposure to Accutane.

(Transparency)

This overhead shows the proportional distribution of pregnancy risk categories of women treated with Accutane, based on national data from the Survey of Family Growth which we used in our model, and based on the Slone study of Accutane, some of the results of which were presented before the Committee this morning.

The main differences between the national data and the Slone data are in the estimates of how many women are abstinent and how many are sexually active but practicing no method of birth control.

There are important reasons to be skeptical of the Slone data and these will be discussed later. However, we concluded it here in this analysis so as to be as conservative as possible in the estimation of pregnancy exposure which results.

(Transparency)

This overhead shows the number of birth defects and pregnancy exposures estimated to have occurred in 1989, based on data from Trussel and Kost, as well as the Slone Epidemiology Unit data on distribution of pregnancy risk categories, and data from the National Survey of Family Growth. So we have the "typical observed", we have our model and we have the "lowest expected".

The estimates provided by our original model are very close to the theoretical minimum which would be observed if we were dealing with perfect users. This is never seen in real world situations. So the actual numbers of pregnancy exposure and birth defects from Accutane experienced in 1989 is probably closer to that of the "typical observed". Realistically speaking, it is quite likely that there were between 76-227 birth defects with Accutane last year.

In our original report, we demonstrated that under-reporting of pregnancy exposure and birth defects was great. This conclusion is not altered by these latest data.

(Transparency)

Regardless of whose data you choose to go with, under-reporting of pregnancy exposure and birth defects was extremely high. At best, only 3-8 percent of pregnancy exposure cases and only 4-10 percent of birth defect cases for 1989 were reported to the sponsor. This is an inescapable reality.

For some, this conclusion is very difficult to believe. People say that physicians would certainly report something as terrible as a birth defect. This a priori expectation is not supported by data or experience.

(Slide)

This slide summarizes the literature in which under-reporting was quantified. All dealt with serious or fatal adverse reactions to drugs in otherwise healthy individuals who were not expected to die. At a time of great interest and public discussion about the risks of oral contraceptives in the United Kingdom, only 15 percent of women with thromboembolic deaths who were taking the pill were reported to the Committee on Safety of Medicines, which is the British equivalent of the FDA.

In another study from the CDC, only 10-20 percent

of sudden deaths in infants, the deaths occurring within 24-48 hours of receiving vaccination with DTP, were reported. Another study from the State of Maryland found that fewer than 10 percent of adverse drug reactions causing death or hospitalization were reported to governmental agencies. A similar level was observed in a study from Sweden.

Dr. Franz Rosa, in our Office, has estimated birth defect reporting with other drugs to be only about 4 percent of actual occurrence.

Finally, we have two anecdotes to relate. About two years ago a child with Accutane-related defects was treated at Bethesda Naval Hospital, which is three miles from where we sit today. This child had been seen and treated by two other physicians before coming to the Naval Hospital. Dr. Peck, our Center Director, saw this child at the hospital and encouraged the physicians there to report this case to FDA. Neither they nor the two separate physicians involved before in this child's case or care reported it to FDA.

The second anecdote relates to the case of birth defect in our Michigan Medicaid study. This case was not spontaneously reported to FDA, nor were any other of the cases of Accutane-exposed deliveries.

Under-reporting is a fact of life which we deal with every day in our work at the Agency. Our observations with Accutane are entirely consistent with the literature

experience.

But why does under-reporting occur? I will begin by asking each member of the Committee to reflect back on their own clinical experience and recall how many patients of yours have experienced adverse drug reactions. Did you report all of these to the FDA? Did you report any of them to the FDA? These are rhetorical questions. In my own clinical experience, I can recall three cases quite clearly of which I reported none.

(Slide)

This slide lists some of the factors known to contribute to under-reporting. Failure to ascertain the drug exposure might be important with Accutane. It is prescribed by one physician specialist and the birth defect is seen by another physician specialist. The physician may not recognize the adverse reaction. In the case of Accutane, if the birth defect were mild or the treating physician was not a trained teratologist, it might not be as readily observed.

From their study of under-reporting in Maryland, Rogers et al. conducted a survey of physician attitudes towards reporting. They found that most physicians felt that they were too busy to report an adverse reaction. Many were afraid of governmental interaction and involvement. The majority did not know where to report or how to report or who to report to. Others were concerned about liability and

others saw no point in reporting known adverse reactions.

(Transparency)

Before concluding, I want to spend a few moments discussing the Slone Epidemiology Unit's Accutane survey. We heard earlier today that they estimate that their projected enrollment in the future will be about 53 percent of women who take the drug. The actual enrollment in 1989 was 28 percent, far too low to provide any assurance of representativeness. Only 19 percent of the patients in the study were enrolled by their physicians, yet, the results which we were shown today are based on data in which 36 percent of the patients were physician enrolled.

As Dr. Mitchell showed the Committee earlier, there are differences in compliance between patients who are physician enrolled and package enrolled. So these biases permeate the entire data which were presented by the Slone group. This has led to biased study results.

For multiple variables reported on, results among the self-enrolled are far less encouraging than those of the physician-enrolled patients. If the package-enrolled patients show poor adherence to aspects of the intervention program, how much worse might be compliance among the 72 percent of women treated with Accutane but not included in the survey?

There are also other problems relating to the way

questions are asked and the way the data are collected, which might yield misleading and incorrect conclusions.

In determining the degree and severity of cystic acne, the survey does not give a clear indication of the actual number, location, severity and size of the cystic lesions. The data which we were shown previously were trichotomized between none, 1-2 and 3+ cysts. Today we saw the data in a slightly expanded form for a more recent interval of time since they have changed the way in which they ask their questions, which showed us that 16 percent of patients had or more cysts.

The design, which applies to the majority of the data where they have trichotomized variables for the number of cysts, will provide which is not of the most utility to the Agency in assessing the severity of disease because it sort of forces one to assume that the category 3+ cysts is severe but that was not the definition of severe used in the premarketing trials. In those trials the definition for severe was 10 or more cysts.

Also the method of questioning in the survey does not permit us to know if the cysts were facial or truncal. This might be important in whether or not one thinks that a risk-benefit analysis on a particular woman is worthwhile.

Another feature is that the Slone study is interventional. There were 32 program failures which were not

discussed very much this morning by the Slone group. These 32 represent patients who were found at T-1, the first interview, to not be practicing contraception and then extensive efforts were made to contact that woman's physician to get her off Accutane or get her on contraceptives.

What we have seen from the data by Trussel and Kost is that in the course of a year 90 percent of those women can be expected to have pregnancy exposure. They have been censored out of the study by the Slone methodology. So the estimate they get for pregnancy exposure will be substantially artificially reduced below that which would occur in 72 percent of women not subject to the same interventional strategy.

Finally, the question about prior antibiotics does not indicate whether dosage and duration were adequate to establish disease recalcitrance. As I pointed out in the Michigan data, we see that prescriptions are frequently of short duration and they are not administered consecutively over time.

In the area of contraception, the survey results are based on women's answers about their contraceptive status on the day of the telephone interview. Dr. Mitchell tells us that T-1, the first interview, occurs at about 1 month after enrollment, which is about 1 additional week after they start Accutane. So 5 weeks after the woman starts Accutane, she is

asked, "On this day, are you using contraception?" And we get results. It does not tell us what they were doing for the previous 5 weeks and that could be very important.

The Slone data have shown that women do change what they are doing. Abstinent women become sexually active; sexually active women become abstinent. They change methods; they drop methods. So there is lots of ambiguity in the way they ask the question and the results, therefore, cannot be entirely trusted.

The same problem also applies to classifying a patient as being sexually abstinent. Abstinence is often intermittently broken. The survey may very well overestimate the size of this group.

Of concern in the Slone data was that 6 percent of women using contraception at the first interview were no longer using it at the second interview. We were not told these data -- excuse me, we were told that today.

(Transparency)

At the beginning of this meeting on Accutane Dr. Nelson went over the current label for Accutane. As you saw then and as I have shown here, that label states that the drug is contraindicated in women unless all of the following criteria are met: That she has severe cystic acne that is recalcitrant to other therapies; that she has had pregnancy testing done by a serum method; that monthly pregnancy

testing is strongly recommended; that she start Accutane on the second or third day of her period.

From the Slone data, these are the percentages observed among the self-enrolled respondents in the study. Compliance with each of the features is poor, at best. If we multiply each of these percentages together, we arrive at the conclusion that Accutane may be contraindicated in over 97 percent of the women entered in the Slone study.

(Slide)

To summarize, Accutane use substantially exceeds its label. Our estimate of disease incidence is under 5000 per year. Yet, last year 65,000 women were newly started on the drug. This level is unchanged from 1989. Since coming on the market, about 1 percent of all women of childbearing age have been treated with a potent teratogen. This represents an extremely high exposure from a public health perspective. Of these women, modeling of pregnancy exposure by multiple methods, conservative as well as more liberal, suggests with a fair degree of certainty that about 3 percent of these women experience first trimester exposure to the drug. This 3 percent should not be so unbelievable.

The sponsor observed a 5 percent rate of pregnancy exposure during its controlled premarketing studies. This was in a setting of informed consent; contraceptive counseling; contraceptive practice and pregnancy testing.

In the study by Dr. Richard Platt, cited in my report, medical record review of all women treated with Accutane in the past 2 years found a pregnancy exposure rate of 2.5 percent. In Michigan Medicaid we found a rate of suspected exposure of 5.8 percent. Later today, Dr. Edward Lammer will present data from California with a rate of 3.1 percent.

From our modeling, we estimate that there have been over 16,000 cases of first trimester pregnancy exposure to Accutane. About 75 percent of this number ended with abortions. We have estimated the relative risk for abortion and found it to be increased 2-fold amount women who use Accutane. Of first trimester pregnancies reaching delivery, up to 25 percent may have a birth defect. In the U.S., modeling suggests that there are over 900 cases of Accutane-induced birth defects. Perhaps half of these children died in infancy. Even using the most conservative estimate available, fewer than 10 percent of these cases were reported last year.

It follows from this that spontaneous reports cannot be relied upon to monitor the extent of pregnancy exposure or birth defects with Accutane. Furthermore, because of problems with program compliance and contraceptive failure, pregnancy exposure to Accutane will occur as long as Accutane is given to women of childbearing potential. The

only way to eliminate pregnancy exposure is to eliminate the use of this teratogen in women of childbearing potential. In a very real sense, pregnancy exposure is totally preventable.

(Slide)

The goals of the intervention program were, one, to eliminate pregnancy exposure and, two, reduce the level of use to that consistent with the disease incidence. Our data and the firm's show that the intervention program has failed to achieve these objectives. It will not achieve them in the future.

The Slone study shows that more than half the women who got the drug did not have severe cystic acne. The data shown this morning showed that at least 40 percent of the women recently enrolled in the study had no cysts. When we multiply all the other factors out accounting for the low compliance with the different features, especially pregnancy testing, we come to the startling conclusion that for most women who got Accutane it was contraindicated for them.

In their presentation, the sponsor tried to discuss in greater depth what they are doing to evaluate the low rate of pregnancy testing reported in the Slone study. They have relied on sort of a mini-survey of physician offices where patients had previously been reported to not have pregnancy tests done. The information obtained was surrogate means. They asked the office manager, who is well aware of what the

liability concerns are and what the requirements are for the appropriate use of the drug. Without medical record verification, including documentation of the serum pregnancy test in the chart, I do not think that these data can be believed with any reliability.

The firm's suggestion that there be a switch to office-based urine pregnancy testing will permit the fudging, if you will, of medical record charts. When you send a blood specimen out and you get a slip back that has the result on it from an independent laboratory, there can be no doubt that the test was done. If the goal is to eliminate pregnancy exposure, then one component of that has to be that the pregnancy test has been done.

From the study done by Richard Platt which we cited in our report, the sponsor said in their critique of our study before this Committee this morning that the data covered a period before the real time. Last week Dr. Platt faxed to us updated data from his plan that covers the time through the end of February, 1990.

In the 10 subsequent months to the data covered in my report, the rate of serum pregnancy testing, validated and verified by medical chart review of patients in that health plan was 60 percent and 40 percent of women did not have a serum pregnancy test. So the data from the Slone study suggesting that there is a high proportion of non-compliance

with that feature are probably accurate.

Accutane cannot safely be given to women of childbearing potential without pregnancy exposure occurring and it cannot be rendered safe. The only way to eliminate such exposure is to eliminate the use of Accutane in women. In the U.S., over 1 percent of all women of childbearing age have received this drug and about 3 percent probably had pregnancy exposure to it. The great majority of these women treated with Accutane and experiencing pregnancy exposure did not have the disease for which the drug is approved. Thank you.

DR. SCHROETER: Thank you, Dr. Graham. We have several items of housekeeping. First, when we reconvene at two o'clock, Dr. Barbara Hulka, who is Chairman of the Fertility and Maternal Health Drugs Advisory Committee, will take over the chair and we will co-chair with her leadership.

(Further housekeeping announcements)

We will see you at two o'clock.

(Whereupon, at 1:00 p.m., the Committee adjourned for lunch, to reconvene at 2:00 p.m.)

AFTERNOON SESSION

DR. HULKA: Good afternoon. We would like to get started; it is going to be a long afternoon. We would like to start the afternoon agenda with Dr. Carl Peck, Director of the Center for Drug Evaluation and Research, and he would like to make a brief comment before we go ahead with the agenda.

DR. PECK: Thank you, Dr. Hulka. We have been queried as to whether the conclusions of the last presentation represent an Agency view in terms of conclusions. I want to state that they do not necessarily represent an Agency view. We actually could not hold that, else, we would not be asking you the questions that we have asked you to discuss.

They represent a very careful, penetrating analysis that Dr. Graham and his staff have undertaken with continuing review within the Office of Epidemiology and Biostatistics. I think I will leave it at that. We are very interested this afternoon in hearing your discussion and points of view on many of the same issues that Dr. Graham brought up in his discussion.

DR. HULKA: We will go ahead then with Sidney Wolfe, from the Health Research Group, who will make a presentation.

PRESENTATION BY SIDNEY WOLFE, M.D.

DR. WOLFE: I would like to thank FDA for asking me

to appear before this Committee. It is either the fifth or sixth time I have appeared before either the Dermatologic Drugs Advisory Committee or the Fertility and Maternal Health Committee separately last year; together now, which probably should have happened a long time ago.

I will just start out by reflecting my own frustration about this whole process. Almost seven years ago we petitioned FDA to stop what was clearly an inordinate amount of over-prescribing of this drug by issuing box warnings, warnings about the Accutane syndrome birth defects; also warning about pseudotumor cerebri, which happens in men and women.

We also urged that a foolish thing which both FDA and the Company had done upon initial marketing of the drug be reversed, which was to delete the requirement that a woman get a pregnancy test before taking the drug. During the clinical trials prior to approval of the drug, pregnancy tests were required. For some reason that does not make any sense at all that was deleted from the package information and from the labeling, and only a couple of years after marketing was it put back in as it had been prior to approval.

Two years ago, feeling at that time that there was no possibility that educational methods, labeling and so forth were going to work, we petitioned FDA to seriously restrict the use of this drug by requiring all doctors

prescribing it -- who, we argued, should be dermatologists -- to sign on a one-time basis a form essentially saying that they agree to prescribe only for the labeled indication for women of childbearing age for severe, recalcitrant cystic acne and, secondly, to do initial and follow-up pregnancy tests. Failure to comply with that would have been criminal penalties as our petition went.

One year after the petition was filed, and after the FDA refused to decide publicly whether they had the authority to implement the restrictions that we recommended, the petition was denied but, interestingly, missing from the response by Dr. Young a year ago was any statement that FDA did not have the authority. We now know that former legal counsel of the FDA, Thomas Scarlett, thought and probably still thinks that the FDA does have the authority to do this but the FDA has failed to get off the fence and say they do have the authority to do it or that they do not have the authority, in which case it would not be difficult to get Congress to give them the authority.

What is the international situation? That has not been mentioned today. I would just like to go over it briefly. In one sense, Accutane represents the drug lag in reverse. It was approved in the United States prior to approval anywhere else in the world after fewer than 200 people in this country had been given drug in clinical trials

for severe recalcitrant acne. Larger numbers have been given for other purposes but for the purpose of discussion today, these were, by and large, small clinical trials.

As I mentioned before, it was approved without any mandatory pregnancy test. They have a warning in here and that was not instituted until afterwards.

In the past two full calendar years, 1988 and 1989, as seen in the first chart, there have been no reported birth defects anywhere in the world other than from the United States. These are the year of birth of the child. The numbers reported in the United States in 1988 and in 1989 are a total of 10 birth defects. But the 1989 data are not complete yet. If last year and the year before is any indication, we can imagine that another several cases will be reported.

Again to emphasize what Dr. Graham mentioned, these are reported cases. They are only a fraction of the actual cases that are occurring. The rest of the world has no cases; the United States has 10 in the last 2 years.

On the second chart -- and all these data are obtained from the FDA -- can be seen the reported rate of serious Accutane birth defects reported in the United States and five other countries. These are 1987 population rates in each of these countries.

What you can see is that the rate of reported

Accutane birth defects in the United States is about twice that of Canada and Switzerland. Canada has the same lack of restrictions, by and large, that we have in the United States. Switzerland is the home of Roche and they treat the Swiss as badly as they do anyone anywhere else in the world, with large amounts of Valium and Accutane floating around the population.

One can see that in the United Kingdom, West Germany and France there is a much lower rate. There is just 1 case in each of these 3 countries of birth defects. The United States rate is 17 times higher than the rate in the United Kingdom and France and 19 times higher than the rate in West Germany, a country which, like the United Kingdom, bitterly remembers the thalidomide tragedy and is determined not to repeat it. Although, and possibly because, thalidomide was never marketed in the United States and we do not have a similar bitter memory of the tragedy of drug-induced birth defects, there seems to have been, and to continues to be, less caution to prevent the Accutane disaster which continues to unfold in this country.

The third chart is 16-39-year old women because this is the way the Company reported the data. These are Accutane users per million total population in those countries per year marketed. So if it is marketed for a longer period of time, that is taken into account.

What you can see here is that the rates in United States, Canada, Switzerland and France, which also has no restrictions, are quite high, much higher than the rates in West Germany and the United Kingdom. The United States rate of 252 16-38-year old women per year of marketing is 9 times higher than the rate in West Germany and 6.7 times higher than the rate in the United Kingdom.

What is the situation now? Well, you have heard several different versions of it this morning. Our version is, I think, very conservative. It probably understates how bad the problem is. As of now, there are a total of 79 serious Accutane birth defects reported in the United States through 1989. As I mentioned before, not all the 1989 data are in yet. It is likely that at least 3 times more have actually occurred, thus, about 237 serious birth defects. It may well be that this is too low an estimate.

As mentioned on one of Dr. Graham's slides this morning, generally for adverse drug reaction reports there is about a 1 in 10 deficiency. We are only getting 1 report for every 10 that actually occur. It might be a little higher for this but it certainly is not to the point where we are getting anywhere near complete reporting; it is a fraction. This is clearly the worst epidemic of preventable, serious birth defects we have ever seen in the United States.

Equally tragic are the several thousand women who

have had induced abortions because they later found that they had been pregnant before they had started Accutane or became pregnant afterwards and were understandably frightened, as the labeling would lead them to be, of the 25 percent risk of a seriously deformed child if they carried the pregnancy to term.

Gross over-prescribing continues despite of, or to phrase it another way, because of the inadequacy of the various measures taken short of severely restricting the distribution of the drug.

These are data that were presented this morning, although they were updated and they are slightly worse than what I am presenting here, in a Roche-funded study, being done on contract to the Slone Epidemiology Unit, in Boston, even with its severe selection bias of who participates -- in other words, the doctors, in our view, who are most likely to participate are the least likely, and it is difficult to prove it, but they are the least likely to be the ones who are violating the conditions of the labeling. Yet, a large number of them were. In the data presented, there is evidence of a large amount of reckless and dangerous prescribing: 32 percent of women of childbearing age who were given the drug and who were surveyed did not have any acne cysts (Roche appendix 2, table 8), with an additional 16 percent having only 1 or 2 cysts. That figure was 40 percent

when presented by Dr. Mitchell this morning. In the same survey, 40 percent of these women did not have any scarring.

Also in the Roche study, it was alarming that 37 percent of the women surveyed did not have a pregnancy test before starting Accutane. There has, if anything, been a slight decrease -- not significant but it is certainly not an increase -- in the percentage of women who had pregnancy tests from early 1989 to early 1990.

Stealing only one number out of Dr. Lammer's presentation out of dozens, if not hundreds, that he will give, even worse misprescribing was found in that of women who unintentionally used the drug, in California, after conception, a majority (60 percent) did not have cystic acne.

In summary, about 50,000 -- this is the lower bound and the other figure of 65,000 is probably closer to it -- women of childbearing age continue to get Accutane each year in the United States. A large proportion of them do not even have cystic acne. Of those who do, it is not clear what fraction have been first tried on other less dangerous treatments and I would add, based on Dr. Graham's presentation, on adequate doses and durations of therapy of the less dangerous treatments, such as antibiotics.

The drug has already caused at least 237 serious birth defects in U.S. children, which continue to occur here but not in the rest of the world. In addition, several

thousand women, 50-70 percent, or according to Dr. Graham's estimate 100 percent more than would have abortions without the threat of a severely deformed child, have had induced abortions.

The current U.S. policy on Accutane which guarantees continuation of preventable serious birth defects and tragic abortions by women who would otherwise deliver a child must be stopped. If the FDA continues its recalcitrant policy of refusing to seriously restrict the availability of Accutane, we will have to consider going to the United States Congress to force the issue, and that is not an idle threat.

I will be glad to try to answer any questions that you have.

DR. HULKA: I think we will have to go on because of our time frame today. What I expect is that, depending on how the time goes, if each speaker uses less than his 15 minutes, then we will have an opportunity for questions. Otherwise, the bulk of our questions and our discussion will have to be at four o'clock.

DR. WOLFE: Did I meet my quota?

DR. HULKA: You met your quota. Thank you. Dr. Ed Lammer, California Birth Defects Registry, will speak next.

PRESENTATION BY ED LAMMER, M.D.

DR. LAMMER: Thank you. I work for the California Birth Defects Monitoring Program. What I would like to

present for the Committee today are some preliminary results of two studies that we have been working on over the last couple of years.

First, a study concerning Accutane use among women in MediCal, in California, which was designed along the same methods as the FDA Michigan Medicaid study, which was initially presented to this Committee two years ago. Largely, this study has been designed to deal with a few problems with that study and also to try and replicate the results in a different population of a public assistance program.

The second study I want to present are some data concerning circumstances surrounding the prescribing of Accutane among 61 women who have actually used it during pregnancy. This group is a subset of the population participating in the longitudinal study of infants exposed to isotretinoin in utero, a study funded by Hoffmann-La Roche through the Massachusetts General Hospital, in which I have been participating since 1985, and from which I presented earlier results to this Committee at its meetings in the previous 2 years.

I should add that the principal investigator on this is actually Dr. Kirsten Waller, who is an EIS officer for CDC assigned to the California Health Department, who is doing this project with me and the MediCal people.

Two years ago Dr. Graham, from the FDA, presented the results of a retrospective analysis of Accutane prescribing among women in a Michigan Medicaid data set, linking temporally the data of Accutane subscriptions with subsequent diagnostic codes for pregnancy terminations, spontaneous abortions and deliveries.

We have attempted to replicate that study in the MediCal population using a similar type of financial data base, however, with what we think are several improvements in study design. First, we have the ability to interview all of the potentially exposed women to confirm whether or not they used the drug after conception, although I must say that that work is still in progress and I only have a small bit of it to present today.

Second, through our population-based registry of all births in California, we have the personnel to send out to evaluate the medical records of these women and children all over the state.

(Slide)

This study concerns all women from age 15-44 who were participating in MediCal in 1987 and 1988. For some of the information we only have 1987 data because we started the project in 1989 and women who were prescribed the drug in 1988 could have used the drug during a pregnancy in 1989. So those data are still incomplete at this time but eventually

we will have them.

In 1987 there were 640,000-some women in this age group in the MediCal system. The prescribing rate in 1987 was that about 2/1000 women in this age group in the MediCal system received a prescription for Accutane.

(Slide)

Dr. Graham has previously gone over the method of assigning potential exposure during pregnancy. I have tried to make it visually a little easier to see. Basically, you take the records showing the date on which the Accutane prescription was filled and a claim was filed. Then for this study we assume a q.d. dosing regimen because these records actually do not indicate whether the prescribed number of pills were given on a b.i.d. or once a day dosage. On that basis, assuming the woman used all of the pills, we can determine an interval when she potentially used the drug. Then using the linked file to the MediCal pregnancy follow-up system, we determined for the same woman diagnostic codes for abortions or deliveries of infants or stillbirths. From the date of diagnosis for abortions, we took the preceding interval of 120 days and for deliveries the preceding interval of 270 days. If this overlapped with the putative interval of Accutane use, this was considered a potential exposure.

Again, the assumptions are q.d. dosage and that the

woman used all of the pills. Also this interval presumes a full-term delivery.

(Slide)

Using the data only from 1987 again because people who were recipients of the drug in 1988 could have gotten pregnant in 1989 and been exposed to a prescription from 1988. So I am only presenting the 1987 data for this piece of information. Using that algorithm, we found 41 women potentially exposed in the first trimester and 7 potentially in the second trimester out of the 3100 users, which gives us a figure of 3.6 percent of these women as potentially having used the drug during pregnancy. This compares with about a 6 percent figure from the Michigan Medicaid study.

(Slide)

For the 1987 data which are complete and the 1988 data which are incomplete, we identified a total of 82 potentially exposed women. Quite surprisingly to us, 60 percent of these women are of Southeast Asian ethnicity. This is a mixed group of women who are Vietnamese, Cambodian, Mong and Laotian. This is highly, highly unusual both for the California population and for women participating in the MediCal program.

We have attempted to verify these pregnancy exposures by interviewing the women. We initially mailed a form through the MediCal program asking them to participate

in the study and to be interviewed to document the exposure. We got back 59 no responses; 15 women refused to participate; and 8 agreed to be interviewed.

Of the 8 we have interviewed, 4 confirmed exposure; 3 had elective abortions because of the exposure and 1 ended in a live birth. We have 4 unconfirmed exposures out of the first 8. One of the women stopped using the drug before conception; 1 was a merging error, an unusual situation where both a mother and a daughter, living in the same household, had the same first, middle and last name. One of them had the prescription for Accutane and the other had the pregnancy. This caused a merging problem within the system. Two of the women, curiously, who had elective abortions denied having them. We are still investigating this to see if this is a situation of billing fraud within the MediCal system or if there is some other explanation, for instance, that they may not have been willing to admit that they had a termination.

Anyway, we did not have very good luck in contacting these people by mail and we now have permission from the Human Studies Committee and MediCal to contact these people to try and interview them in person. This is taking a lot of time because if anybody has ever tried to do a study where 60 percent of your participants do not speak very much English and you have to translate questionnaires into Mong, Cambodian, Vietnamese and Laotian, it is a lot of work. But, clearly,

you do not have to be Yogi Berra to figure out that this is potentially an explanation for why these women may be using Accutane after conception. A lot of them, we suspect, do not speak or understand English very well.

(Slide)

Among the 41 women from 1987 whom we linked to their outcomes of pregnancy -- these are the 41 women potentially exposed in comparison to the outcomes of pregnancy in the rest of the MediCal system -- this is the maternal age-adjusted relative risk for delivery, abortion and spontaneous abortion. Basically, what we see here is that among the potentially exposed women there is a statistically significant excess of elective abortions and an excess which did not reach statistical significance for the women having spontaneous abortions. So, overall, among the women we identified as potentially exposed, they have different outcomes of pregnancy from the rest of the MediCal population.

I should note that in comparison to the Michigan Medicaid study, they had similar findings with an excess of elective abortions and spontaneous abortions but their relative risks were a little bit higher, I think, here. They found a relative risk of around 2 for therapeutic abortions and around 2-3 for spontaneous abortions.

(Slide)

For the live births that we have identified from

1987 and 1988, we have sent people out to review the maternal records and the records for these children. From the finding of 13 live births from the first trimester exposures, we have identified 1 child with malformations. In the second trimester exposures, we have a second child with a malformation that actually is an unusual one but one we have seen among autopsied infants with other major birth defects associated with Accutane exposure.

So in conclusion, 3.6 percent of women potentially using Accutane in the MediCal system may have been exposed to Accutane and 60 percent of these women are of Southeast Asian ethnicity, which is highly unusual. Our data currently verifying these exposures are very incomplete. We have found an increased relative risk for abortions.

(Slide)

I want to quickly present the second study. This is a group of 61 women. Unlike the data you heard this morning, these are actually data from interviews with women who have gotten pregnant on Accutane, comparing women who got pregnant in 1982-1987 compared to women who got pregnant in the last 3 years. Basically, the prescribing in both groups is by dermatologists. That is no great surprise.

(Slide)

There are even lower numbers compared to the data Allen Mitchell presented, we find that in both periods only

about 40 percent of the women whom we have interviewed who have gotten pregnant on this medication were either told by their physician that they had cystic acne or, else, by their description had ever had cysts, nodules or boils.

(Slide)

We asked the women whether the information regarding the risks for birth defects was adequately presented by the prescribing doctor and they said yes. You can see that the numbers have improved over time. Still, in the last 3 years only 60-some percent of the women feel that they got the information presented to them adequately in an oral fashion. This does not include management issues, which we will get to.

(Slide)

Did the prescriber ask about sexual activity? That is improving also. Did the prescriber recommend contraceptive use? You can see that there has been a significant improvement among this group of women during the last 3 years and 88 percent of them now who have gotten pregnant were recommended to use contraception. If they were recommended, did the physician specifically talk to them about the types of contraception? That is still in a significant minority.

(Slide)

Were women actually using contraception? In the last three years, of the women who got pregnant while using the drug, only two-thirds of them were actually using contra-

ception but that is better from the previous time interval.

(Slide)

Did the prescriber arrange pregnancy testing before Accutane therapy began? In the last 3 years only about 40 percent of these women had pregnancy tests before they were put on medication.

(Slide)

To summarize this, for the group of women whom we have identified and interviewed in 1988, 1989 and 1990, how could these exposure pregnancies potentially have been prevented? First of all, 60 percent of these women did not have cystic acne and probably should not have been placed on the medication in the first place. Of the women who had cystic acne, this percentage, which I believe is 10 percent of the whole population, had no pregnancy test performed. They were actually pregnant before they began their prescription. Had a pregnancy test been done, they would have avoided the exposure. One woman was not using contraception. Another was one of these situations that has been discussed earlier of a woman who was properly managed and then went off the drug for a long time and started taking it again without her doctor's management and was not using contraception. Then we have another group, about 20 percent of this whole population, who had contraceptive failures that ran the whole gamut from condoms to oral contraceptives to spermicides.

That is all I wanted to present today. I will be happy to answer any questions later on.

DR. HULKA: Thank you. We will go on to Dr. Jane Adams, from the University of Massachusetts, in Boston.

DR. LAMMER: I am going to present a little introduction to Jane's talk since we are collaborating on this project.

We presented some of our data previously from a prospective cohort of children whom we followed since before birth. That is, we identified a cohort of about 60 of 70 women who had used Accutane during pregnancy and where we had identified those pregnancies before the outcomes were known. That is, they were identified to us before any ultrasound procedures in the pregnancy was conducted. They were followed through the pregnancies. The kids were examined at an earlier age and now we are going back to follow them up at age 5 with a battery of developmental tests to assess outcomes of behavior, socialization and intellectual function.

This group represents the unbiased spectrum of effects of the drug because they were ascertained prenatally. We have evaluated all of them in an extensive protocol of hearing evaluations, eye exams, several hormone assays involving calcium metabolism, and all of them have been examined at least twice during their first five years of life.

The data Jane is going to present are some of the findings from our neurodevelopmental follow up at age five. In particular, we are interested in seeing whether children who were exposed to the drug in utero, who do not have obvious major anomalies, have central nervous system deficits that would predict that they will have problems later in life. The biologic plausibility behind this is that the most common major anomaly induced by the drug is on the central nervous system. So it only makes sense that this drug is likely to cause effects on brain development that are manifested by subtle effects in learning disabilities, lowered IQ and behavioral problems. Jane will now present some of those data.

PRESENTATION BY JANE ADAMS, Ph.D.

DR. ADAMS: As Dr. Lammer indicated, given that one of the manifestations of Accutane teratogenicity is effects upon the central nervous system, it is essential then to look at the cognitive status of the children who have been prenatally exposed. So we have looked at the full sample of the individuals who are now 5 years, plus/minus 3 months of age. So between 4 years, 9 months and 5 years, 3 months. These children have been given a cognitive assessment to make this determination.

I should also indicate that there is a wealth of animal data and other human data that suggest that functional

problems do occur with increased incidence even among children who do not have major malformations. So that was one of our questions in this group.

(Slide)

So far, we have seen 32 isotretinoin-exposed children and 24 matched controls, all from a prospective sample. The children were between 5 years, plus/minus 3 months, when tested and a battery of neuropsychological tests is used. This battery includes the Stanford Binet IV, which is the most recently standardized measure of general intelligence which is available. It also includes a variety of measures which are being used to look at things such as attention, memory, linguistic ability, visual perceptual processing and motor function.

Before presenting the results, which are going to be limited today to the general mental index, the Stanford Binet IV, I would like to give you a little bit of information about the construction of this test and what a score means.

(Slide)

The Stanford Binet IV, like all of the major IQ tests in use, has been standardized and normalized, such that the average score is 100 and a standard deviation is 15 points. If an individual scores less than 70 on this test, meaning more than 2 standard deviations below the mean, that individual falls into the mentally retarded category. If an

individual scores between 71-85, that is one of the ranges of subnormal intelligence, designated borderline intelligence. A score between 86-115 is average; 116-130 is designated as superior intellectual functioning and above 130 is the gifted category.

(Slide)

So restricting ourselves now to the subnormal range of intelligence, which is individuals scoring in the borderline to mentally retarded range, 52 percent of this sample of isotretinoin-exposed children are falling in that range of general mental functioning. So 52 percent of the children have borderline to mentally retarded intellectual functioning versus 8.4 percent of the controls -- clearly a significant increase in this category.

(Slide)

To break this down further and to look then at borderline and mentally retarded categories separately, the data are provided in this slide. In the category that is the mentally retarded range, 19 percent of the isotretinoin-exposed children are falling into this category. In the borderline intelligence range, 32 percent of the isotretinoin-exposed children are functioning at this level.

As you can see, there is a general increase in the number functioning below normal and a general decrease in the number functioning in the average to above average ranges.

(Slide)

It has also been of interest to us to determine the relationship between major malformation and functional status because one question is to what extent you can predict outcome based upon status at birth and those things that can be detected at birth.

This slide indicates the proportion of individuals in each of the functional intelligence categories that have major malformations. All of the mentally retarded children were also found to have one or more major malformations. In the borderline intelligence category 40 percent of the children have major malformations. You can see that the percentage declines as functional status improves. In the average range of functioning, 8 percent of the children had major malformations.

The important point about this slide is that while major malformations are associated with increased risk for poor mental functioning, they are not the full explanation. There are children in all categories of functioning that have major malformations and, indeed, many more children are cognitively impaired than the number who have major malformations.

So the point is then to hope that you will include in your judgment of adverse outcome not just major malformation status but also functional status. Children who are

functioning in the subnormal range of intelligence are not capable of going to regular public schools. They need a great deal of support in order to function. The children in the sample that are functioning in the mentally retarded range are severely mentally retarded, most of them being institutionalized and, at the age of 5, not yet having the motor development to support holding up their head or their upper trunk; not having developed any language yet -- at the severe end of the spectrum.

So in closing then, 52 percent of the children are functioning in the subnormal range, whereas, a smaller percentage have been shown to have major malformations. I will be happy to answer any questions later on if that is appropriate.

DR. HULKA: We will change the order of presentations here slightly. Dr. William Scott, of the Teratology Society, will present at this time.

PRESENTATION BY WILLIAM SCOTT, D.V.M., Ph.D.

DR. SCOTT: Thank you. Ladies and gentlemen, I am here today as a representative of the Teratology Society. The Society is an amalgam of clinicians, basic researchers, industrial scientists and government scientists who have, as a common goal, the prevention of congenital malformations. Thus, the exposure of pregnant women to isotretinoin is of concern to the members of the Society since removal of this

exposure would prevent the birth of some malformed infants.

Prevention of birth defects known to be induced by chemical agents has proceeded at a pace less than hoped for. There is consensus that ethanol exposure during pregnancy is damaging to the embryo or fetus. There is similar consensus that certain anticonvulsant agents induce congenital malformations.

In each of these examples there are obvious significant hurdles in removing the agent so that the women are spared exposure to such agents during pregnancy. This same type of dilemma presents itself regarding exposure to isotretinoin. Here we have the case of a drug which has unique therapeutic efficacy against a significant human disease. Yet, exposure to the developing human embryo will usually lead to an undesirable outcome, be it abortion, congenital malformation, retarded growth or decreased functional performance, as you have just heard.

The public affairs committee of the Teratology Society is attempting to tackle this dilemma and provide official Society position papers regarding isotretinoin. Toward this end, a document has been prepared by the committee recommending that isotretinoin distribution be limited to designated centers, staffed by physicians trained specifically in the criteria for prescribing isotretinoin.

In addition, it is recommending that postmarketing

surveillance be implemented to determine the circumstances responsible for inadvertent pregnancies during treatment with isotretinoin.

These recommendations were submitted to the council of the Teratology Society, who agreed in concept with these recommendations, but asked for some revisions which have not yet been completed and which strike at the heart of some of the difficulties of managing the risk associated with isotretinoin exposure.

For example, they agreed with the limitation of distribution, assuming that this does not unduly restrict access of the populations in need. There should be special consideration given to treatment of males and of females beyond their reproductive years. Could a limited distribution scheme disenfranchise certain populations, such as the poor, those in inner city areas and teenagers?

It is obvious that there must be a continuing search by Hoffmann-La Roche, the FDA and other interested parties to find a means to effectively prevent exposure of pregnant women to isotretinoin. The manufacturer has already mounted a large program toward this end which relies on voluntary compliance of physician and patient. If the concept of voluntary compliance is unsuccessful, there is the alternative of mandatory restrictions instituted by the manufacturer, as has recently been done by Sandoz in the

marketing of their product, Clozaril, used to treat schizophrenia.

Questions such as these regarding management of risk lead directly back to assessing the magnitude of the risk. There can be no doubt that isotretinoin exposure, at usual therapeutic dosage during the early stages of human pregnancy, can result in abortion or congenital malformation. Lammer and his associates have estimated that 25 percent of children exposed to isotretinoin are born with congenital malformations and now there is emerging evidence that prenatal isotretinoin exposure can lead to intellectual deficits in children without structural malformations.

Thus, it seems only prudent to assume that isotretinoin exposure during early gestation will adversely affect most pregnancies.

The question then becomes how frequently exposure during pregnancy occurs. Here the quantification of risk becomes less clear as we have only estimates of varying or unknown reliability regarding, one, how many women of childbearing potential actually take isotretinoin and, two, how many of these women are or become pregnant while taking isotretinoin. Precise information on these parameters would help identify the magnitude of the problem that must be managed.

The purpose of my visit is twofold. First, I am

here to keep abreast of the programs designed to minimize exposure to isotretinoin during pregnancy and of the attempts to elucidate the bases for non-compliance with the physician and package instructions. It will be my responsibility to report these findings to the public affairs committee and the Teratology Society at the annual meeting next month.

Certainly, this report will influence the position taken by the Society in a public stand they will adopt regarding isotretinoin availability, presumably in the near future.

Secondly, and equally important, I am here to remind the Committee that the Teratology Society is deeply concerned with the problem of isotretinoin exposure during pregnancy and renew our offer to provide expertise in developmental toxicology. Thank you.

DR. HULKA: Since you have been so prompt in your presentation, let me ask any members here of both Committees if they have questions of Dr. Scott, Dr. Lammer and Dr. Adams because there was some inter-relationship among these presentations. Yes, Dr. Niebyl?

DR. NIEBYL: I just have one question. When you talked about populations not using contraceptives, has anyone looked at whether these patients have been sterilized or their partners have been sterilized; if they have had a hysterectomy -- things like that? It seems to me fairly

striking to see such a large percentage not using contraceptives when there are all these warnings all over the packaging now to advise against that. There must be other factors explaining some of that at least, I would think.

DR. SCOTT: I would defer to Ed. He might have a better reply than I could make.

DR. LAMMER: Yes, I think it is a very complicated situation. Some of the women we have identified fall into the situation that has been discussed here earlier today of people who were put on medication and may or may not have been managed appropriately through that. Then they go off the medication and then they have some pills leftover at home and they take those without supervision. That is a common situation we have seen where people have not been using any contraception at all.

A second woman, whom I interviewed only two weeks ago, said that when she was prescribed the medication she told her physician she could not take oral contraceptives. I do not remember the reason; it might have been hypertension or a previous problem with them. The physician who was prescribing the drug made no other suggestions about what kind of contraception she might use. So she tried rhythm and was not very successful.

DR. NIEBYL: So that points to lack of counseling.

DR. LAMMER: Yes.

DR. NIEBYL: But there is a free trip to a gynecologist.

DR. LAMMER: Of all the women I have interviewed, I have never talked to a single one with whom the physician even discussed that program. I think Allen Mitchell's data shows that 25 percent of women are aware of it. Those are preliminary data as well. But the population I am talking about is a select group. These are not all the women who are being prescribed the drug. These are the women who have gotten pregnant on the drug. But that is the group that clearly we need to focus on because it is important to know exactly how they got pregnant and what the circumstances were. Their circumstances may not be applicable to the whole universe of people in the United States.

DR. DAVIDSON: I have a technical question. In the next to the last presentation discussing the developmental effects, I thought that was emphasizing developmental abnormalities without structural abnormalities. Could I see that last slide again? It seems that the slide showed something different from what I heard in the presentation and I just want to get that straight.

(Slide)

Is the grey part the malformations?

DR. ADAMS: Yes, the part that is hatched is the number of children in the category that were identified to

have one or more major malformations. The sample was the whole sample, all prenatally exposed children, regardless of outcome.

DR. DAVIDSON: And your interpretation was that most of the severe developmental disabilities were without malformations?

DR. ADAMS: No, the conclusion is that knowing that a child has a major malformation does allow you to predict that that child is at increased risk but it does not do it 100 percent of the time. There are individuals with major malformations who are functioning in the average to above average range and there are individuals without major malformations who are cognitively impaired.

DR. DAVIDSON: Thank you.

DR. HULKA: We have another question over here. Dr. Woodley, did you have a question?

DR. WOODLEY: I did but Dr. Lammer went on and emphasized that his data were derived from people who were failures on the drug.

DR. SCHLESSELMAN: I have a question for Dr. Adams relating to the nature of the control series in her study. If she could just speak to the matter of how the controls were selected and then, secondly, whether the evaluation of IQ was done in a blinded fashion?

DR. LAMMER: I could probably better answer that.

First, these children reside in more than 25 states and Puerto Rico. We do not actually have any Canadian kids in this study in the data that were presented. So selection of controls is a problem. The controls are age matched. Both the exposed kids and the controls are within three months of their fifth birthday at the time we do the evaluations. The way we identify control children, since every child we see is in a different city in the United States, the selection method we chose is to contact the primary care physician for the exposed child, in most cases a pediatrician. We assign them a letter of the alphabet and ask them to go to that letter of the alphabet and sequentially identify children who would have a birth date that would fall in the age range in which we want to do the evaluation. Then we ask them to sequentially contact those parents and ask them if they would be willing to participate in the study as one of the comparison children.

That is the method we chose. It is not as perfect as we would like but it is very difficult to do this kind of a study when you have children in 25 different states and you only have 1 person to examine in each city. That is basically how we selected the control group. So they are age matched and they are physician matched, which probably carries along with it unintentionally some socioeconomic matching as well.

DR. WOODLEY: You did not answer if it was blinded

though.

DR. LAMMER: Yes, Dr. Adams does her evaluations blind to exposure status. For kids who are severely affected, clearly that does not work and I do not know any way to get around that, although in one case one of our control children ended up having cerebral palsy and is in a wheelchair. I do the best I can to keep her blind during her evaluations. I am not blind to exposure status since I have to go through the permit process with families, etc., before Dr. Adams does her evaluations. So she is blind to exposure status throughout her evaluations.

DR. TSCHEN: I have another question. There is anecdotal evidence that Accutane might increase the fertility of the patients using the drug. In the patients for whom you had the opportunity to review the contraceptive methods, is there any such instance?

DR. LAMMER: I would say the answer is absolutely. I am convinced this drug has fertility-enhancing properties. That is another circumstance that goes to the question previously about why some of these women are not using any contraceptives. I think we have identified close to ten women now who have gotten pregnant on the drug who were not using contraception because they had long-standing histories of infertility. The causes of infertility ranged from DES effects to endometriosis to undiagnosed causes of infertility.

We have gotten the story so many times now -- it is anecdotal but I think there is something to it, that the drug does enhance fertility.

There is evidence in experimental animals that vitamin A is necessary to promote reproduction in animals that are maintained on a vitamin A-deficient diet and are infertile. But we have not found a consistent pattern of causes of infertility that are associated with these exposed pregnancies.

DR. DAVIDSON: I have a question of Dr. Wolfe but I would like to respond to that comment. Although I think it is kind of dangerous to start speculating on the effects of infertility and sexual behavior, I would not ignore the fact that if a woman had pustular acne and it started getting better and she started feeling better about herself and how she looks -- that may have a lot to do with the kind of relationships she forms. And that is as much science as what was offered before.

(Laughter)

We have a large number of congenital abnormalities in this country, probably a background rate of 2 or 3 percent and maybe somewhere in the neighborhood of 100,000 to 125,000 out of the 3.8 million births. There was a comment made, I think by Dr. Wolfe, that this was the most dramatic demonstration of congenital anomalies that has been known. That

may or may not be true but I just wonder, understanding the amount of abnormalities as a perinatologist, that we potentially engage in, in terms of anticonvulsant therapy, the number that may be associated with anticoagulants, the number that may be associated with oral antihyperglycemic therapy of diabetics, some of the antibiotic concerns, the issue of methotrexate which is often used in pregnancy, and other antimetabolites that are used in leukemia and other chemotherapy -- I just wonder, just for purposes of accuracy, should we consider this the most potent teratogen that is used in prescription medicine?

DR. WOLFE: What I said was that it was the most preventable. I did not say it was the worst. For exactly the reasons that you have stated, I think that the odds of someone getting methotrexate or anticonvulsant medicine who should not be getting it is nowhere near the odds of the large number of women of childbearing age who should not be getting Accutane because they do not even have cystic acne.

So I was really focusing on comparison with all of the other known major causes of birth defects and this one is very much more preventable and, hopefully, that is what is going to be done this afternoon.

DR. HULKA: We will go on at this time. Dr. Peter Pochi, from the American Academy of Dermatology, please.

PRESENTATION BY PETER E. POCHI, M.D.

DR. POCHI: Madam Chairwoman and members of the Committee, I am Peter Pochi. I am an M.D., dermatologist, Professor of Dermatology at Boston University School of Medicine, in Boston. I am chairman of the task force on acne and Accutane under the committee on guidelines of care of the American Academy of Dermatology. I am pleased to represent the more than 8000 dermatologists of the Academy today.

I appreciate the opportunity to once again talk about isotretinoin or Accutane. First, I would like to discuss the importance of the drug and, second, to review with you the actions that the Academy has taken and is still taking and, third, to offer some recommendations for changes in the current prescribing practices for Accutane that could serve to lower the incidence of pregnancy in women treated with this drug.

I do not intend to detail in length the utility of Accutane for acne as this would be, for the most part, an unnecessary exercise. You are familiar with the outstanding therapeutic effect that is achievable with this unique drug. I must, however, emphasize two distinctive and telling therapeutic features of Accutane. The first is that it can be extraordinarily effective, no matter how severe the acne or how treatment recalcitrant it is.

(Slide)

Let me show you a series of a very few cases

quickly. This is a patient with cystic disease before treatment --

(Slide)

-- and after a course of Accutane therapy. The patient is left with a few scars but it is essentially an excellent response.

(Slide)

This is an individual with acne combined with rosacea, not an infrequent combination. You see the large lesions here.

(Slide)

And after 16 weeks there is a remarkable change.

(Slide)

This is probably the worst case that we studied when the drug was in the NDA. This individual had severe nodulocystic disease.

(Slide)

After 20 weeks of therapy there is complete eradication of the disease but, again, leaving scars.

The second point is that after a course of Accutane is completed -- and you have heard this before -- which is usually 16-20 weeks in duration, the clearing of the acne, which is almost invariably the outcome, is maintained with no further treatment of any sort for prolonged periods of time and occasionally with no recurrence whatever. All other

treatments for acne, even when they are effective, do not alter the natural course of the disease which can persist for years.

(Slide)

It should be further stressed that since most cases of severe acne, and many cases of less severe acne, can result in permanent damage to the skin, either as atrophic, shown to a moderate degree here and here -- and this individual does not have cystic acne but certainly has severe disease --

(Slide)

-- and this patient with scars that should never have occurred and would not have but this picture was taken in the pre-Accutane era.

(Slide)

Occasionally hypertrophic scars develop. These are even worse in a sense, although less frequent. These cause a severe psychological impact upon the patient because these can last for decades after the disease process itself has become inactive.

Unquestionably, the best treatment for such scars, mostly of the atrophic variety, as shown in the previous two slides, is the prevention of their occurrence which, of course, is what happens with Accutane.

The problem, as we all know, of course, is that

Accutane is a teratogenic drug. The Academy has consistently stressed this danger with the drug's manufacturer and will continue to do so. Nonetheless, the members of the American Academy of Dermatology, experts who know this disease, its natural history and the too frequent ineffectiveness of alternative therapies for severe acne, conclude that the benefit-risk ratio justifies the present and continued availability of Accutane with appropriate warnings and precautions against pregnancy during therapy.

Although the Academy's earlier educational efforts were described before both Committees, permit me to briefly reiterate just two of them:

In May, 1988, a "dear colleague" letter was addressed from the Academy's president to the entire Academy membership discussing FDA's concerns and announcing the appointment of a committee, which I chaired, to develop guidelines on the use of Accutane. These guidelines were formulated, approved by the board of directors of the Academy, mailed to the entire Academy membership in August of 1988, and were published formally in the November, 1988 issue of the Journal of the American Academy of Dermatology, which has a worldwide circulation of 12,000 physicians and medical libraries.

In March of 1989, the Academy again wrote to the entire membership asking for its cooperation in the Slone

Epidemiology Unit study of female Accutane users, which enrolls such patients, tracks their progress and evaluates the effectiveness of the FDA-Hoffmann-La Roche pregnancy prevention program.

Other Academy efforts since the last hearing include the following four: Firstly, the American College of Obstetricians and Gynecologists, in cooperation with the Academy, is revising a patient information brochure on contraception. The brochure presents birth control information in a concise and non-judgmental manner. The importance of not being pregnant while on Accutane will be incorporated into this patient information vehicle.

Secondly, the Academy, again in cooperation with the American College of Obstetricians and Gynecologists, is developing a physician counseling video, entitled, "Counseling Dermatologic Patients on the Use of Contraceptives." This video is scheduled for release this fall. The complete educational package will include the video, the Accutane guidelines, a video summary and a quiz for category 1 CME credit.

An educational grant will allow for an all-member mailing of this educational package. This mailing will also be provided to more than 100 dermatology residency training programs, with a letter urging that the video be incorporated into the training program.

Thirdly, in March of this year, the Academy convened a consensus conference for the defined purpose of delineating severity levels of acne. Noted experts in the field of acne from the United States and abroad attended this conference. A consensus statement is currently being drafted. When completed, the outcome of this conference will be published and distributed to the Academy membership.

Lastly, in the April, 1990 issue of the Journal of the American Academy of Dermatology the Academy republished the guidelines for prescribing Accutane in the treatment of female acne patients of childbearing potential.

These activities are part of the Academy's continuing efforts to ensure that Accutane is not administered during pregnancy. Yet, on the basis of available evidence to date, it appears that the incidence of pregnancies in patients undergoing treatment with acne has not been reduced to a near-vanishing level.

Despite this, the Academy remains unalterably opposed that Accutane be withdrawn from the market. To do so would deprive all patients, not just women of childbearing potential, of the enormous benefit of the drug's alleviating a socially stigmatizing disorder. Moreover, such a draconian measure would, undoubtedly, lead to patients obtaining the drug by illicit means and, worse still, using it without medical supervision.

A second course of action could be the restricted use of Accutane to designated medical centers, a position that the Academy also cannot support. Apart from the unwieldy logistics involved, wherein many patients would need to travel great distances on at least half a dozen occasions, the patient is put at additional risk when side effects from Accutane occur that require hands-on management. The patient's dermatologist, or any other physician experienced in the treatment of acne and the use of Accutane, should be the individual responsible from beginning to end for the decision to prescribe the drug and for monitoring closely the patient's progress throughout the course of therapy.

However, we would favor consideration of the following: Point number one, that the drug manufacturer's prescribing information in the drug package insert reinforce the monthly test for pregnancy during Accutane treatment, as already stated in the Academy's guidelines.

Point number two, that the patient information consent form that is in the drug manufacturer's pregnancy prevention program kit be changed to require not only that the patient and physician complete the form, but that the patient also be required to enroll in the surveillance program.

Point number three, that a special Accutane prescription form be devised and used for dispensing the drug

to females of reproductive capacity, in which the physician checks three boxes, indicating that a consent form has been executed, that a blood pregnancy test has been performed at the appropriate time and with a negative result, and that contraception has been discussed with the patient.

Only when the prescribing physician has attested on the Accutane prescription that all three conditions have been met will the pharmacist be able to fill one or more prescriptions of the drug to women of childbearing potential.

These last two points are severe and precedent-setting measures and it could be argued that they are not necessary. But Accutane must remain available to acne patients who, as I mentioned earlier, can be physically and emotionally affected and devastated and possibly scarred for life by the disease. Dermatologists are sensitive to the issues being raised at the present time concerning birth defects. The American Academy of Dermatology continues to work closely with Hoffmann-La Roche, pediatricians, obstetricians and other health care professionals to prevent birth defects from occurring.

We are convinced that the actions already taken, our continuing educational programs and the recommendations we are now making address emphatically the critical issue of preventing birth defects while still allowing patients with severe treatment-resistant disease to have ready access to

this highly valuable drug.

On behalf of the members of the American Academy of Dermatology, I wish to express my sincere thanks for being allowed to address you today.

DR. HULKA: We will continue with Dr. Mary Spraker, from Emory University.

PRESENTATION BY MARY K. SPRAKER, M.D.

DR. SPRAKER: I speak today as a concerned dermatologist, pediatrician, practicing academic pediatric dermatologist and a mother as well. Because I have trained in both pediatrics and dermatology, I feel I understand the issues as they pertain to both fetus and the woman with acne. I am also the current chairman of the American Academy of Dermatology's task force on pediatric dermatology, although in this forum I am speaking as an individual and do not represent the AAD.

To severely restrict distribution of Accutane or to withdraw it would belittle the suffering caused by patients with severe acne. Severe acne is not a lethal disease but it does profoundly affect lives. All of us remember friends and acquaintances with severe acne and what it has done and continues to do to them as individuals.

Fortunately, it is now fairly uncommon for most of us in our everyday worlds to run across patients and people with severe acne. Why? Because Accutane's effect has been

truly miraculous. The patient who does not respond to antibiotics will usually respond to Accutane after one relatively brief, 16-20-week, course of treatment, after which the drug is discontinued. Most patients remain in permanent remission.

There is no drug more satisfying to prescribe and no patient more grateful for treatment. I can quite literally change a patient's life. Unfortunately, the drug is a teratogen and the age group afflicted with the acne is also at higher risk for pregnancy.

It was known at the time the drug was introduced that it was a teratogen in animals and that it was not to be used during pregnancy. This was emphasized by Roche. When, unfortunately, pregnancies did occur, confirming the human teratogenicity of the drug, we, in dermatology, were certainly made aware of this development. For example, at our annual national meetings, which are attended by 80 percent of practicing dermatologists, there was great discussion regarding what could be done to prevent future pregnancy exposures.

Our goal is to decrease the number of pregnancy exposures to as close as zero as is humanly possible. But how? One obvious answer is to only treat patients who need the drug, namely, patients with severe acne who have not responded to more conservative therapy. It has been suggested

previously today and in other years that the drug is overused. Approximately 63,000 female patients are treated annually. Since there are approximately 6200 dermatologists in the United States, that means that each dermatologist treats approximately 10 patients a year or slightly under 1 patient per month.

We could argue that about half the dermatologists may be working part time; they may be in academic centers and are not treating acne patients. So possibly we could project that the average practitioner might treat 20 female patients per year. Since most practicing dermatologists see a fairly large number of acne patients, it does not seem unreasonable that this proportion of patients would need Accutane.

More accurate epidemiologic data regarding incidence of severe acne unresponsive to antibiotics would certainly be helpful. The past suggestion that Accutane usage be decreased by 20 percent is arbitrary. The drug has never been approved for mild acne so which of my severe patients do I not treat and what do I say to that individual patient?

I have an ethical and potential legal dilemma when I face the female patient who has severe acne and who needs Accutane. What can I do to make sure my patient does not become pregnant? I certainly warn her and the pregnancy prevention program has made this easier. After the patient proves she understands the pregnancy problem by passing the

quiz that she is required to take and sees the pregnancy contraindicated symbols stamped all over her package of pills, I feel it is not possible for her not to have gotten the message. This makes me feel better.

I emphasize the need for excellent contraception. I mention the known failure rates of contraceptions, even when properly used, and advise a visit to the gynecologist, which Roche pays for, to reinforce my instructions. FDA approval of more effective contraceptives would be helpful.

But is it ethical for me to insist that every patient take an oral contraceptive, even if she insists her current contraceptive is adequate or that she is not sexually active? Occasional patients develop serious complications from oral contraceptives. Shouldn't the patient have a right to participate in this decision?

I then send the patient to the lab for baseline liver function tests, triglycerides and a serum pregnancy test and I instruct her not to take the Accutane until the second or third day of her next menstrual period. But now there are some logistical problems that I think are worth mentioning. Do I give her a prescription for one-month supply of drug at that time? Or do I call in the prescription after her labs are back or normal? Or do I call in the prescription in only after she calls me to tell me that her menstrual period has started? Or do I have her come back to

the office to document that, yes, she is menstruating and repeat the pregnancy test to rule out mid-cycle spotting?

None of us wants to demand unnecessary office visits, labs and the expense they entail. These questions are important because at least some of this year's pregnancy exposures were when patients were already pregnant when the patients began treatment with the drug.

Education of physicians regarding their proper use of Accutane is very important. We certainly will continue to work on that. But no matter how carefully we instruct, we are dependent upon our patient following our instructions. As physicians, we can guide our patients but we do not have and do not want power to control them. We should respect the fact that patients must take some responsibility for the treatment of their disease.

This leads me to voice concern regarding proposals to limit treatment to regional centers which, I feel, would be counterproductive, as well as logistically difficult. An important aspect of pregnancy prevention is not only assessing the patient's disease but also establishing a good patient-doctor relationship. By personally seeing a patient multiple times in the past as traditional antibiotic therapy fails, the local physician does have the opportunity to get to know the patient, establish a good relationship which, hopefully, will help the patient follow through with the pregnancy

prevention program.

Another drawback to the center approach is that there have been documented pregnancies in the past when the drug was limited to center use. During the clinical trials of the drug when it was on IND status, there were a number of pregnancies.

One could argue that eight or so years ago, when this occurred, the severity of the teratogenicity was not recognized so pregnancy prevention was not emphasized, as it is now. But in talking with one of my colleagues at another university who participated in these trials, he, personally, was very concerned about the teratogenicity of the drug at the time since it is a vitamin A relative. He included a statement in the consent form that his patients signed and emphasized carefully to each of his patients the pregnancy problem. He also is a person who establishes good rapport with his patients. Despite this, two of his patients became pregnant and these were college-educated patients who, he felt, had understood.

Never in the history of drug prescribing has more been done to educate physicians and patients regarding the teratogenicity of a medication. This is good and may be helpful as we look at other substances with serious side effects. Teratogens, such as Dilantin, alcohol and over-the-counter vitamin A, more commonly have serious side effects,

such as anaphylaxis from penicillin. The patient information methods we created together are truly innovative. Yet, if we proceed, we need to take great care because the decisions we make regarding Accutane will have important ramifications for many other medications, both old and new. Decisions must be made on data and not speculation. Thank you.

DR. HULKA: Thank you. We will go ahead. Dr. Jose Cordero, Centers for Disease Control, will speak at this time.

PRESENTATION BY GODFREY P. OAKLEY, Jr., M.D., M.S.P.M.

DR. OAKLEY: Jose Cordero is not speaking because the airplane did not get here in time. My name is Godfrey Oakley, Jr., Director of the Division of Birth Defects and Developmental Disabilities, Center for Environmental Health and Injury Control, at the Centers for Disease Control, in Atlanta. I am a pediatrician, an epidemiologist and a geneticist.

The mission of our program is to search for causes of birth defects and developmental disabilities and to prevent unnecessary morbidity and mortality due to these conditions.

Birth defects and developmental disabilities caused by in utero exposure to Accutane are at least as severe as, and occur as often after exposure as those caused by thalidomide and rubella infection. Twenty-five percent of those exposed have obvious birth defects that include fatal and

severely disabling cardiac and central nervous system birth defects. Recent evidence suggests that at least 20 percent of those born without birth defects have a developmental disability. Unlike most birth defects, defects and disabilities caused by exposure to Accutane are totally preventable, yet, they continue to occur.

None of us wants a single baby to be born wit a birth defect or a disability caused by Accutane. At the same time, we want anyone who has an approved indication to be able to get Accutane. Because contraceptive measures fail, babies damaged by exposure to Accutane will continue to be born as long as Accutane is available. I am here, however, because I believe that we can reduce significantly the number of babies born with Accutane damage.

(Slide)

The number of babies damaged by Accutane can be very substantially reduced by two primary prevention strategies that have not been effectively implemented. One is to reduce to a minimum the number of fertile women who take the drug. The other is to minimize contraceptive failures. This slide shows the impact of two variables on the number of babies born with birth defects and developmental disabilities caused by in utero exposure to Accutane. These two variables are, one, the number of exposed women and, two, the type of contraceptive selected.

This graph shows our estimates of the numbers of live-born babies that would be affected by Accutane for varying numbers of drug users. Along the horizontal axis we show different levels of use per year from 4000 to 70,000 women of reproductive age. We also show estimates of the number of Accutane-damaged babies born for 3 different yearly rates of contraceptive failure. This would be 20 percent, which is the usual rate for spermicides. The blue is 3 percent which is often associated with oral contraceptives. The yellow is 0.3 percent that is the approximate failure rate for injectable or implantable contraceptives like Depoprovera or Norplant.

The assumptions for this slide are detailed in an attachment to my written statement. We believe these assumptions are reasonable. For example, we used the manufacturer's observation that approximately 50 percent of exposed women that were reported to them elected to continue the pregnancy. We also used Dr. Lammer's observation that 25 percent of exposed fetuses are born with birth defects.

As you can see, one way to lower the number of Accutane-damaged babies born is to reduce the number of women of reproductive age who take the drug. The best evidence suggests that only 4000 women a year have an approved indication for taking Accutane. About 70,000 women of reproductive age take the drug. If only 4000 women of

reproductive age took the drug annually and if they were not pregnant when they started the drug, and if they used a contraceptive with a failure rate between 3-20 percent, we would expect, on the average, the birth of 2-13 Accutane-damaged babies each year.

On the other hand, if 70,000 women of reproductive age continue to be treated and their rate of contraceptive failure is between 3-10 percent, then each year we would expect the birth of between 33-221 Accutane-damaged babies.

This slide also shows that using a contraceptive with the lowest failure rate would also reduce the number of Accutane-damaged babies being born. The most effective contraceptives are injectables and implantables.

Those who are interested in reducing to a minimum the number of Accutane-damaged babies being born would want a reliable surveillance system. A reliable surveillance system would identify accurately all exposed pregnancies and follow and report in a timely fashion the outcome of those pregnancies. None of the current efforts has provided a reliable, timely surveillance system.

Clearly, we have the opportunity to reduce the number of babies being born with damage caused by Accutane. If we immediately reduce the use of the drug among fertile women to the 4000 a year who have an approved indication, and if we immediately provide them the best contraceptives, we

could, 9 months from now, have a substantial reduction in the rate at which Accutane-damaged babies are being born. If we provide a surveillance system for exposed pregnancies that is active, timely and highly reliable, we will be able to document this reduction.

Those of you who can take the actions that would result in a greatly reduced number of Accutane-damaged babies being born may be interested, as I was, in a report that appeared in the May 14th, 1990 issue of The Wall Street Journal. The report, which appeared just last Monday, describes the actions that Sandoz took voluntarily because the Company had a drug that was useful in the treatment of patients with schizophrenia but which, like Accutane, caused some of their patients treated with it to die. A copy of the article is attached to my written statement.

To quote from the article, the heart of this system consists of "exclusive contracts with Baxter International Inc's Caremark home-care division to take weekly blood samples from each patient and to dispense the drug, and with Roche Biomedical laboratories Inc., a subsidiary of Hoffmann-La Roche Inc., to analyze the blood for white cells. No other company, agency or hospital can deliver the medicine, and each patient has to submit to a blood test each week."

The article also states that Sandoz estimates the market to be 70,000 patients. I do not know whether all the

statements in the article can be supported by evidence. Those who have the responsibility for taking the actions necessary to prevent the birth of Accutane-damaged babies might find it helpful to talk with Sandoz officials.

I thank you for your attention and the opportunity to be here. My colleagues and I are willing and eager to help you in any way that we can with the primary prevention of the birth of Accutane-damaged babies. I would be happy to answer any questions.

DR. HULKA: Thank you. We have one additional person who has requested to make a very brief statement, Dr. Harold Kaminesky, of the American College of Obstetrics and Gynecology.

PRESENTATION BY HAROLD KAMINESKY, M.D.

DR. KAMINESKY: Thank you very much, Madam Chairman. I will stay here because my remarks are brief. I am the director of practice at the American College of Obstetricians and Gynecologists and I would simply like to make a statement that it is the position of ACOG that drugs that have important therapeutic indications should not be restricted categorically because they may be teratogenic.

To restrict them categorically immediately limits their use for those patients for whom they are indicated. I need not express to this audience the fact that generally means the socioeconomically disadvantaged by income, by

geography and so on.

We have heard excellent presentations of the problems with Accutane and also the importance of the drug in treating young women, a small number of whom require the drug because of a very disfiguring condition.

Dr. Pochi has pointed out that we have joined with the American Academy of Dermatology to produce a videotape that will be made widely available to dermatologists and, I take it, to other physicians who may be treating patients with Accutane and who, for one reason or another, are also going to be in a position of having to describe and prescribe the method of contraception. This will, doubtless, be of some help.

I would point out again that one would not expect that in a single year one could see the result of an educational campaign of the kind that has been mounted by the American Academy of Dermatology and Roche. I would expect that it will take a lot more time before we will have achieved a reduction in the use of this drug, one, for women who do not require it because they really do not have cystic acne and, two, for contraceptive methods to be applied carefully to all those women who require it.

Nonetheless, it is the position of our committee, and it certainly does not have an executive board decision because it would be inappropriate for us to do that, that it

would be inappropriate at this time to either remove the drug from the market or restrict it categorically.

DR. HULKA: We have a few minutes remaining until the designated break time. Do we have questions? Yes, Dr. Davidson?

DR. DAVIDSON: I would like to ask a question of any of the dermatologists. If there were not -- and I know how artificial this question is, but if there were not the concern about the fetal abnormalities, what then would be a reasonable range of indications for this drug? I am concerned about the assumptions that are made as to how well one could expect the restrictive nature of the indications to be complied to in a disease that seemingly has such potential prospective psychological effect and people do not want it to progress, certainly, to the stages of cystic severe disease.

DR. SCHROETER: Dr. Pochi, you represent the AAD's position on this drug and I think you might be the one, representing that constituency, to give an answer to Dr. Davidson's comment and question.

DR. POCHI: Well, first of all, although teratogenicity is the central issue and the most important in terms of side effects of the drug, there are other side effects as well. These should be carefully monitored. Dr. Spraker referred to doing blood tests, measuring blood lipids and liver enzymes. There are lots of other side effects that are

in the arena of high dose retinol therapy -- pseudotumor cerebri. These are rare and can be followed. None of the side effects are cataclysmic.

So even if this drug were a non-teratogen, it simply would not be used like water. It would, however, be used the same way that it is used now. In males the drug is used in patients who fail traditional forms of therapy. Therefore, this drug still is a last resort drug for acne in any patient who has disease that is severe or less severe but is unresponsive to traditional therapies and even some non-traditional therapies.

DR. WOODLEY: First of all, I think that is a very good question, and also what about the woman who does not have cystic acne by the criteria of the original indications for Accutane when it was originally presented to the FDA? Let's say they do not have ten bad, horrible cysts but let's say they have severe recalcitrant, debilitating acne which is not necessarily cystic but has been proved to be unresponsive to enormous measures, and they have had it for many years and have been on systemic antibiotics and have failed to respond? That might be what you are really focusing on.

DR. DAVIDSON: Yes.

DR. SCHROETER: There is another response to that question. In 1982, when this drug was labeled, although teratogenicity was paramount in FDA's and Hoffmann-La Roche's

writing of the label, it was not as of considerable importance as it is now. If you go back to that labeling, the indications for use are restricted to those patients who have severe recalcitrant cystic acne or acne that is not responsive to other conventional use of drugs. I think that will tell you the perspective that it has been used in and I doubt that that will change.

DR. POCHI: May I comment on your comment? I think the reason originally that the drug did not receive as much concern about teratogenicity was the fact that, while it was a teratogen, the doses that were required to produce teratogenicity in animals far exceeded those in milligrams/kilogram for man. I know that many of us who experimented with the drug were rather convinced that the drug was not going to be teratogenic. The manufacturer, to their credit, very carefully warned about the possibility that the drug was teratogenic. We were more concerned really about the other side effects.

Dr. Woodley's question about the patient who does not have severe cystic acne but has, as he mentioned, ten horrible cysts, which was the minimum criterion that we used when the drug was under an IND and NDA testing, in actuality, they did not have to be horrible cysts. They had to have a minimum of ten "cysts" -- a bad term, by the way, because the term nodule is much more appropriate and this will ultimately

be expunged from the literature because they are not cysts. The lesions had to be only 4 mm in diameter or larger and did not have to be at one site. They could be spread on the face, back and chest. So when these patients were studied, in actuality, they did not have to have severe cystic acne; just ten lesions anywhere. They could have three on the face, three on the chest or on the back.

However, as it turned out, because there were so many patients who had severe disease, and I think still do, the vast majority of patients had very severe disease, with the average number of "cystic" lesions exceeding 25.

I would guess, although I have no proof for this, that a substantial number of patients today do not have severe cystic acne as you view it in your mind -- "acne horrible". Many of the patients who are treated have acne that is moderately severe but has scars associated with it or who have resisted all forms of therapy.

The only indication that really still holds is the recalcitrance. The severe cystic acne part certainly applies to many patients but there are also patients who have moderately severe acne and it goes on and on and on. It resists all therapy and I am sure that this is the reason that these numbers are higher than many people would like them to be when they quote figures of 4000 and 5000 patients with cystic acne. This would be a partial explanation for

why more patients are receiving the drug than some would like.

Let me point out, however, that there are no data that are reliable on the incidence of cystic acne in women. The NHANES data have been repeatedly referred to. I do not want to take the time to explain the foibles and fallacies of that study but I would be happy to do it privately or at a later time.

DR. HULKA: Thank you. I suggest we have our break now and come back here so that we can start at four o'clock. That will be the discussion for the two Committees.

(Brief recess)

DR. HULKA: Thank you. We will reconvene now for the last hour. I would point out the two basic questions that we are asked to address. One is really a discussion item on our reaction to how effective the sponsor's program has been to date in informing physicians and patients about the risk to the fetus if a woman takes Accutane while pregnant. So that is how effective has the program been to date?

Then, depending on how we respond to that, do we recommend additional measures be undertaken? There is a listing of possible kinds of additional measures but certainly there may be others. That is not an exhaustive list.

Those are the two areas that we are to consider. By the way, is restricted to Committee members and other

folks here at the table.

Does anybody have a burning question, point, or whatever that he or she would like to bring up on the information we have heard? Yes?

DR. WOODLEY: I would just like to ask who has written the questions before us and who is specifically asking those questions in the FDA?

DR. HULKA: Well, they do come from the FDA.

DR. WOODLEY: It is a big place.

(Laughter)

Whose hot little hand had the pen when they wrote those questions?

DR. BILSTAD: The questions represent a number of meetings that we had prior to this meeting, input from a number of different sources. As a matter of fact, we went through a number of different versions of the questions. I was certainly involved in the final wording of the questions but there were other people who were involved as well.

DR. DAVIDSON: Since ultimately numbers and how they change will determine, to some extent, the effectiveness of any program since reduction in the numbers is what the goal is, after listening to the discussions, I really raise the question of whether or not it is reasonable to shoot for a goal of 4300 new patients per year, as I understand this disease and the interest both on the part of the patient and

the physician who treats it. So I first raise the question whether or not that basic assumption should not be challenged.

DR. HULKA: Would the dermatologists want to speak to that? Yes?

DR. ABEL: I have some difficulty with that figure of 4300 from the HANES study. I participated in that HANES study in a small way as a resident. As a practicing dermatologist, however, and one who is not in an active practice seeing patients every single day, I know in any one year I see a number of patients with nodulocystic acne, a number of patients who are candidates for Accutane treatment. If there are 6500 dermatologists in the country, it seems to me that figure is on the very low side and perhaps some of these patients may not have 10 or 15 cysts but may have a very scarring, disfiguring form of acne that may interfere with their lives socially, economically and physically and they deserve to be candidates. So I do question that figure.

There seems to be an issue of perhaps documentation as far as prior therapy; the duration of prior antibiotic therapy; the number of different antibiotics tried. Certainly, the documentation could be there -- should be there.

Also I raise the question of photographic documentation. Certainly, that is something that could be done. Patients could be photographed prior to treatment and after treatment to document that they have severe cystic or

scarring, disabling type of acne. Thank you.

DR. HULKA: Since there is quite a bit of question about actually how many patients would be eligible for treatment and a suggestion that maybe the numbers that have been thrown around here on the basis of NHANES being too low, would anyone have a suggestion as to how a truer number might be obtained?

DR. WOODLEY: I heard at lunch today that there is another HANES-type study being planned by the government. But I understand that dermatology is not represented and that there will not be a skin exam in that, and that is too bad.

DR. NIEBYL: I have just a couple of comments about the recommendations that we have heard about with regard contraception and pregnancy tests. In fact, we have heard quite often that patients given Accutane had not had pregnancy tests or had not been using contraception. I guess I wondered if that was ever put in clinical perspective. If a patient came to my office and told me that she had been on birth control pills for three years and she continued on her birth control, I am not sure that it would be cost effective to have monthly pregnancy tests on that woman.

For that matter, if the dermatologist prescribing the drug talks to the patient and she has recently seen a gynecologist for contraceptive counseling, that may be why some patients did not go to the referral program or did not

ask about contraception.

But, yet, there are other groups of patients that really need very detailed contraception counseling. For example, it seemed to me that the group of women abstinent on this drug was fairly high. The patient who says that she has never had intercourse or has not for years and she does not need contraception -- that is the very one that may very well need it. Her acne gets better and three months or four months later she really feels better about herself -- we know that many of these pregnancies are from unplanned intercourse. That patient needs contraception more than any and she should be sent to the gynecologist for education or birth control pills as a treatment for acne, or however you want to get her on the pill.

DR. HULKA: Well, the current program is that Hoffmann-La Roche will pay for referral to the gynecologist. Are you suggesting in any way that this should be beefed up or altered?

DR. NIEBYL: I am just saying that if the problem is unplanned pregnancies, if patients are not using contraception because they are abstinent, that is the group that still needs to see the gynecologist and have contraception available to it, whether it is education about having a diaphragm or whatever. They ought to know that many women who get pregnant by accident have completely unplanned

intercourse. It is particularly in this abstinent group. It is teenagers who have been previously abstinent or have infrequent partners who, while they are on Accutane, need the contraception. Whereas, the woman who is effectively using contraception already is not at very much risk.

I guess I question even the need for pregnancy testing in that group. But somebody has to discuss with her that visit to the gynecologist; the reasons for it and how important it is. As someone pointed out already, doing the monthly pregnancy tests only picks up after the fact. She is already at risk if she has a positive test, with the possible exception of the baseline test. I will not argue with that because you can have some patients that you might pick up unexpectedly that way. But to do monthly tests really seems hardly worth it when you are just going to detect an already exposed pregnancy.

DR. STEIN: I would sort of like to pick up on that comment and I would like to propose that the second course of counseling by a second physician is reinforced, is strengthened and emphasized, particularly perhaps in a younger patient who might tend to be slightly more non-compliant. To reinforce that would be valuable.

DR. NIEBYL: The other issue is counseling in foreign languages. If a patient is Cambodian or Laotian and you are giving her an English blister-pack with English

warnings, that is not going to be very effective. I noticed that they do have Spanish in their pregnancy prevention program. Maybe something could be beefed up for some of these other languages in California for these patients at risk.

DR. HULKA: I think that is a good point. I think something else we should keep in mind is that most, by far the most of the data we have seen today are data that were collected prior to May of 1989 when the information for the prevention program really went into effect. So we have had a relatively short time, less than a year because I believe the most recent data we saw were through March of 1990. So it has been a relatively short time to see the effectiveness of that patient kit. Anne Wentz, did you have a comment?

DR. WENTZ: No. I wanted to bring up the 60 percent of Southeast Asian babies and thought that that might be a hot spot for identification, not only of a patient population at risk but perhaps a group of physicians who have perhaps inadequate prescribing habits.

DR. POMERANZ: I was on the Committee when Accutane was initially approved, about seven or eight years ago. I think that the present program that was initiated about a year ago probably will be helpful but it is not effective enough. I think more has to be done. I would strongly endorse the recommendations from Dr. Pochi via the American

Academy of Dermatology. You ask how can we get real numbers of the patients who require this drug. The only way you are going to get them is by mandatory registration into the surveillance system.

The second thing, of course, is that after it has been determined that the patient does need the drug, then I think the prescription blank that has been suggested, with the patient saying that she consents, that she has had a blood test for pregnancy and that contraception has been discussed -- I think those things will really have an impact. I think that it is important that the FDA do that.

DR. HULKA: So just to make sure I understand you, you are recommending a mandatory surveillance program?

DR. POMERANZ: The same thing that Dr. Pochi suggested, if I understood him correctly.

DR. SCHROETER: The American Academy of Dermatology task force, as represented by Dr. Pochi, has made a clear and distinct change of posture even since May 10, the document that was sent in your packet. He gave that pronouncement and I think that maybe that should be reiterated at this particular time. I am going to read from that statement. I am going to read all three of these recommendations:

One, that the drug manufacturer's prescribing information in the drug packet insert reinforce a monthly test for pregnancy during the Accutane treatment.

Two, that the patient information consent form that is in the drug manufacturer's pregnancy prevention program kit be changed to require not only that the patient and physician complete the form, but that the patient also be required to enroll in a surveillance program.

Three, that a special Accutane prescription form be devised and used for dispensing the drug in which the physician checks three boxes, indicating, (a) that a consent form has been executed, (b) that a blood pregnancy test has been performed and is negative and, (c) that contraception has been discussed with the patient.

The Committee may not want to endorse all three of these but I think the second is a very common position we have gravitated to, as I have talked to members of the Committee and to those constituencies that have presented today.

DR. HULKA: I see a lot of comments in response to this. Why don't we start on this side of the table and go around?

DR. FLEISS: I am not sure that those recommendations go far enough. I think the success of education is what we have seen, which is some step forward but there is more to be done and I do not think further instruction, further education or reinforcement will do it.

I have heard arguments that the 4500 new cases per

year is all wrong and that prescribing is not being done too frequently. But all the numbers that I have seen suggest the opposite, that there is over-prescribing. One of the recommendations that we make I think has to be what do we do to make a dent in -- what to me is a fact -- the over-prescribing of Accutane.

DR. HULKA: But, Dr. Fleiss, let me ask you if physicians, along with their patients whom they put on the drug, in essence, who are now going to submit a form as part of a registry mechanism -- do you think that might have an effect on prescribing?

DR. FLEISS: Who will look at that form and what auditing mechanism will be put in place to make sure that what is on the form is accurate? I can fill out forms from now until doomsday.

DR. SCHROETER: Well, there is a response to that. The patient is consenting to submitting data and those data will be open vista. Indeed, it will be documentation that may lead to medical-legal defense or to counsel.

Number two, it is a post facto peer review system. In other words, after the fact the physician will be reviewed by his peers in the surveillance. So it does make an impact.

One of the issues that I think was very well put is that the physicians and patients who enrolled in the Slone Epidemiologic study were the ones whom we probably do not

need to reach, whereas, the number two measure requires all patients and, therefore, we may reach those physicians who are more or less procrastinating in this type of registration and not participating on a voluntary basis.

DR. WOODLEY: I, like many reasonable folks, do not believe the HANES study very much and do not really think that is a good basis for the incidence or prevalence of cystic acne. Therefore, I think we really do not know how much over-prescribing is really being done. The jury is still out.

I think as a Committee, or maybe the FDA, we could ask in the next HANES-type study that skin be examined and maybe concentrate on this particular issue; maybe pay less attention to eczema and psoriasis this time around and really focus on what the true incidence of cystic acne is. I saw a lot of heads nodding and so I think everyone would think that would be a useful thing for us to do as a Committee.

DR. NELSON: I would be interested in hearing from the representative from the Academy of Dermatology. The Slone study showed that approximately 15 percent of all patients enrolled in the study were enrolled by the physicians. That translates to a much lower percent as you consider all the persons being prescribed Accutane. How are we going to get from something less than 10 percent to 100 percent? I am missing how we are going to do that. How are

we going to get the dermatologists to comply with this new requirement?

DR. POMERANZ: It seems to me that he is going to have to comply. It is going to take a very reckless physician to have a special prescription form for Accutane and just fill it out in a casual sort of a way because the patient will not get the drug unless he has it filled out correctly. That will automatically, in addition, register the patient with Hoffmann-La Roche. So I think it will have an impact on the physician. I doubt that you will ever get 100 percent of anything but I think you will, in that manner, get their attention more, and more of them will register the patients directly themselves.

DR. WENTZ: The guidelines that Dr. Pochi presented, I believe, are valid ones to discuss but only if we make the stipulation that consent has to be given and received in the patient's own language.

DR. HULKA: Jim, did you want to say something?

DR. SCHLESSELMAN: I would just ask a question of those who recommend patient enrollment in surveillance as to what would be the consequence of that with regard to providing something other than a name. What other additional information will be required? Simply to provide a patient's name, in and of itself, does not do very much for a surveillance system. Is the physician or patient, by enrolling in such a

surveillance program, giving consent to have her records eligible for scrutiny by the Slone Epidemiology Unit and become part of the study? What are the consequences of that?

DR. NIEBYL: If I could just comment on that, it seems as if part of the consent form the patient ought to agree to is to be contacted and give the appropriate data, when it is decided what you want to find out, as part one of that consent form. That would be just like signing a consent form for any follow-up research study.

DR. DAVIDSON: I have a couple of questions about the recommendations from the task force in dermatology. I agree with the objections about the monthly test. I think it would be much more of value to be more specific and lay more stringent conditions about the first pregnancy test because, seemingly, a number of patients are getting the drug and they are already pregnant. I think something should be done to avoid that. Once patients are counseled etc., I would be less concerned about the monthly test.

With regard to the prescription check-off, I would suggest that if there were a check-off, everything that needed to be checked off, including whether or not a pregnancy test or contraception had been done, would be included in the check for consent.

There are some serious issues of confidentiality being raised by these, not only in terms of the patient and

the physician relationship, but I would submit to you that there are some issues about confidentiality about sexual behavior that seem to be important to Americans that are not being discussed by this. This is a serious, fundamental encroachment, both in terms of the relationship between the physician and the patient, and almost constitutional rights.

Nobody is more concerned about birth defects and infant deaths than I am. But this is the kind of regulation with which the West would never have been won.

(Laughter)

DR. BARBO: If women of childbearing age are not the ones with this problem, who are they? So how can we restrict women of childbearing age from having this drug? I do not see who else, of women, would really be appropriate to treat.

My concern is where is the failure. Is it physician failure or is it patient failure in following through? I suspect we have some of both and we have to tighten up the regulations and the way we prescribe it and what the patient understands. I think a lot of things we have talked about are good. I am against having information on a prescription form as well, which breaks patient confidentiality. But I think that we probably do not have adequate consent forms.

Every day when I do informed consents, many patients do not want to hear all those things and a lot of patients

cannot read the consent. They do not read at the level at which many of them are written. I wonder if we should not add a film which might be more graphic and might be in the spoken word and, therefore, more understood by patients than just the written consent form.

I do not know if it is legal to require them all to agree to the study or not or to enter into it. I think that is another real question which I have. But it does take time to do an informed consent and I think that is where we need to put most of our emphasis to patients.

The last thing that I think we need to do is collect the unused medicines. Patients still continue to save some for the next episode, be it urinary track infections or whatever they think is going to come down the road and happen to them in the future. As we heard today, I am concerned about the patients who save some or give it to their friends or relatives. It is in those patients that we have no information given and no informed consent that we have catastrophes.

DR. STEIN: As far as the language barrier, perhaps as part of this, if Roche does go ahead and puts a jacket around the preexisting package there could be some symbolic way of conveying the message that if there are questions, it would be easier for the patient to get answers to those questions if perhaps an 800 number with a question mark on it

could be printed in large type on the outside of the package, and some mechanism set up for patients who do speak different languages to have access to that number.

It is not going to be easy. None of this is easy. Dr. Davidson raises some important concerns. This is all logistically perhaps a real nightmare but I think, at the very least, we need to track things more closely to get more information as to what is going on and to not have a lot of drug being given out to people's friends and relatives which, as we all know, happens with prescription drugs.

DR. HULKA: Could I just make a comment here? I gather there is desire for a more complete surveillance system. The problem that we have seen with the existing prevention program is that information appears to come back, or is likely to come back on about 50 percent of actual women using the drug. Is this one of the problems that you are expressing? No? That does not seem to be it, okay.

DR. WOODLEY: There are two different issues here. One is trying to make sure everyone crosses their t's and dots their i's. The other one is a research question. If you get a study where you have a 55 percent response rate, that is a pretty darned good sample if you have 31,000 people. I do not have trouble with that. I think we have to really be sure what we are talking about, whether it is oranges or apples.

DR. HULKA: We disagree on that point. There are problems with a 55 percent response rate and what it means in terms of selection. That is always a problem.

DR. WOODLEY: Yes.

DR. SCHROETER: Well, you are not only talking about research surveillance, you are talking about trying to limit the drug to those people who need it through a surveillance program that is required. We know that if something is required by physicians and is put in the labeling by Hoffmann-La Roche, more than likely the physician will pay heed to it since that is a guidance that will be medically-legally referred to. It does not restrict the use of the drug though.

DR. HANEY: I would be very surprised if anything on a prescription would fly through the legal department. But I think what will probably fly is a consent document, signed by the physician who prescribes the drug, as well as the patient. The issues that you want about not being pregnant and maintaining contraception -- even if I am not sexually active now but will become, or did become, etc. -- all these issues can easily be put in a consent document that both the patient and her doctor sign. She has a copy. And if there is a more powerful thing in American medicine than an attorney, I do not know what it is.

I am impressed that motivation to do it well and be sure she is not pregnant when she gets the drug, which

actually was one of the largest groups, would certainly go a long way to eliminating that, and I do not think that is going to violate anybody's rights.

DR. POMERANZ: I think that that consent form would then have to be given to the pharmacist before he gives out the drug.

DR. NIEBYL: Well, he can be another check.

DR. POMERANZ: The consent form indicating that all these things have been done, before the pharmacist can dispense the drug, he has to have that form.

DR. HANEY: I do not believe that is possible.

DR. POMERANZ: Why not?

DR. HANEY: Because patient confidentiality would not allow that identification. I just do not believe that is possible. No consent form that I ever give a patient to sign goes outside the hospital or my office record, which is a far different level of confidentiality than drug records.

DR. POMERANZ: Well, we are at a level that I do not know anything about.

DR. HANEY: That is a legal issue.

DR. POMERANZ: Maybe we cannot solve that but it seems to me that that would cut down over-prescription of the drug. Physicians would think twice before turning that in to somebody else. Maybe it would have to be sent to Hoffmann-La Roche and they would send out a thing that they have reviewed

this; that they have recorded it. I mean these people have generally had the disease for a long period of time before they are put on the drug. It is not a decision that is made lightly and if you wait for a month or two more, that is not the end of the world. Maybe sending it to Hoffmann-La Roche is the way to increase the surveillance. That would get the physician's attention too. Then Hoffmann-La Roche would send something back to the physician or to the patient saying that they can now order the pharmacy to now dispense the drug.

It is intrusive and nobody is very happy about that, admittedly, but, on the other hand, if you quadruple or even increase by seven times the number of patients with cystic acne, seven times five is still 35 and there are 65,000 women of childbearing age getting the drug. I cannot believe that all 65,000 of those have recalcitrant acne. I just have difficulty with that at this point.

DR. NIEBYL: I am still concerned about the ones that we saw who were contraceptive failures. The part three recommendation stated that contraception has been discussed. I do not know whether that means by a gynecologist or by somebody who does that every day. But I am not really expected to make the decision on whether the indication for Accutane is there or not in terms of the type of acne and I think it is hard even for someone experienced to discuss contraception with a teenager who has never been sexually

active, or contraception with somebody who has been using, say, condoms and you try to explain to them that that has a higher failure rate than birth control pill. I think to encourage referral to somebody who can sit down and make the whole purpose of that visit the contraception issue -- I am not sure it should be mandatory but to ask a dermatologist to do it is, I think, really difficult. It takes a lot of time and a lot of background preparation to properly say to a woman, "Look, if you've been using rhythm backed up by condoms and you haven't gotten pregnant for the last two years, that isn't good enough. If you're going to take this drug you have to take pills or use two types of methods." You have to have some discussion to really drive home the point that it is unacceptable to get pregnant on this drug.

I would encourage a much higher percentage of referral, not necessarily even to a gynecologist but maybe a family practitioner who does family planning all the time, but not just to somebody who is not comfortable talking about sexuality with patients. I see this all the time with internists who have not felt comfortable in discussing this because they do not do it every day as we do.

DR. DAVIDSON: I agree with Jennifer about most things. I am surprised that she is saying something right here that I do not 100 percent agree with. But this business about requiring a particular form of contraception is another

ticklish area. There are large populations of people that you have to respect about what kind of contraceptive program they are going to participate in. Maybe abstinence and rhythm, or whatever, is the only thing that is reasonable for them to accept. I think they have to be informed --

DR. NIEBYL: That is all I am saying, just inform them that it has a higher failure rate than some of the other methods.

DR. DAVIDSON: Well, I am just saying that there are some other considerations here of people's religious and other beliefs. That is the reason that this across-the-board kind of regulatory approach is difficult.

I would concentrate on the informed consent and certainly patients who are already pregnant. There is a big burden on unwanted pregnancy and the inadequacy of contraception in this country that is unfair to be placed on any single drug because it happens all over the place.

DR. WOODLEY: I tend to agree with Dr. Davidson because if we accept the model of the OEB people that we would cut out in one fell swoop by one-third people if we really concentrated and focused on the initial pregnancy test before being put on the drug -- as I remember, their model had one-third of the persons being pregnant at the time of the medication. Another one was actually a problem with informing the patient by the doctor. The third one was the contra-

ceptive failure. I think it is the third one that we are not going to get around, no matter what we do. But the other two we can have a shot at.

DR. STEIN: Just one more point about confidentiality, again, I agree that it is difficult but I would like to point out that it is done with certain blood tests, as with HIV testing, at least in the State of New York. It is a cumbersome system; it is not easy. Of course, we are talking about one state and we are talking about things that cross state lines here so legal and other issues may come into play. But at least in the State of New York confidentiality is protected and, I assume, in other states also. But I am not familiar with other states.

DR. DAVIDSON: But it is not mandatory to have the test.

DR. STEIN: That is a valid point, yes.

DR. POMERANZ: It is not mandatory to get the drug either. I do not think someone has a constitutional right to a drug that produces birth defects and that they do not have to give up a little something for it.

DR. HANEY: They have the same right that anybody else has.

DR. POMERANZ: They can turn down the drug if they do not want to participate in --

DR. HANEY: You cannot do that. We have to get

into reality here, and the reality is what we can do to lower birth defects, and that is not going to be reality legally.

DR. POMERANZ: The reality is that you are still getting a fair number of birth defects --

DR. HANEY: No argument --

DR. POMERANZ: -- and who is going to take care of those kids?

DR. HANEY: But the most enlightening information we have heard today was where they came from. They came from women who were already pregnant, number one. I think everyone at this table agrees to make an effort educationally and get a pregnancy test ahead of time. The second largest group was women who were contraceptive failures and we are not going to change that. That is not going to be altered by what we do today. So that is the number two group. Then there is illicit use and a few other odds and ends that you can focus on. But, clearly, if you have a document that the doctor signs and the patient signs, wherever it resides in her record, that verifies that he talked to her about contraception; got a negative pregnancy test and she understands the hazard, that will go a long way to forcing the physician, from a variety of perspectives such as medically-legally and the FDA, trying to make sure it happens.

DR. POMERANZ: But the point was made that dermatologists probably are not terribly comfortable discussing the

ins and outs of contraception.

DR. HANEY: Those who are not can refer them to a doctor --

(Laughter)

DR. POMERANZ: I think you will find the average anesthesiologist would also be equally uncomfortable discussing contraception with a patient, or the average surgeon.

DR. WOODLEY: You know, I really liked you before you said that.

(Laughter)

DR. HULKA: Anne Wentz, did you have a comment?

DR. WENTZ: It is just a little point. Even your pregnancy test within two weeks of starting the drug is not going to get you off the hook because a number of patients will still start the drug when they are early pregnant. So it gets to be more and more difficult.

DR. POMERANZ: I see nothing wrong -- maybe I will raise your hackles again but I see nothing wrong with a mandatory visit to a gynecologist. In other words, before a patient can get the drug, they have to have a discussion with a gynecologist as a backup.

DR. HULKA: We have heard this discussion quite a bit. Subir Roy wants to make a comment and then I think we need to change our direction.

DR. ROY: I think we can perhaps utilize the video

that is being formulated by the American College to address the specific issue. Then we will not have to consider whether dermatologists are comfortable speaking about contraception or not because it should be available. It should be brief and to the point and everybody can use that as part of the inherent check list on the informed consent as well.

DR. NIEBYL: Maybe the dermatologists can at least say to the patient that Roche is going to pay for that visit. Maybe that is part of the information that should be on the consent form, "I'm aware that I can get a contraceptive visit for nothing", or something like that.

DR. HULKA: Let me try to summarize what I think I heard that most people have agreed with. By the way, we are talking about question two. We can come back to question two after I make this statement. I want us to go back to question one but these are the things that I think most people have agreed with. So please tell me if you do not agree with these points.

The first point was that we want to emphasize that first, initial pregnancy test. Do whatever needs to be done to ensure that that pregnancy test is done.

Then we want to minimize use of residual drugs, leftover drugs that people pick up later on.

We want to emphasize informed consent, particularly

for people who are not very literate or not very good at English words. We want video information. We want other kinds of information, other than just written English words.

Then we want to encourage and maximize the use of a referral physician, be it a gynecologist, family planning clinic, family physician, whoever.

Those are areas that I heard various people mention and I did not hear many arguments about those points. Does anybody argue about those points?

DR. MCKAY: I think you should add development of other language. A video in English for Laotian women might not be very helpful.

DR. HULKA: Right. So the video might be in different languages. Those were general kind of points that do not have a regulatory vein. But we will come back to question two.

We pushed ahead without addressing question one. I think, in fairness to Hoffmann-La Roche, they have implemented a pregnancy prevention program. As I say, the last phase of that, the patient portion of that went into effect in May of 1989. We have heard about 10 months maybe of data, 9 months of data, in other words, what has happened since then.

So we are asked, and I would like to get some input from you, to evaluate the success to date of the special efforts, initiated in 1988 but actually the second part in

1989, by the sponsor to inform physicians and patients of the serious risks to the fetus if a woman takes Accutane while pregnant. Does anybody have comments on that?

DR. SCHLESSELMAN: I would like to say that, for myself, I do not believe that we can evaluate the success of the intervention efforts. What we can evaluate is to look at what they have done. I would make a personal statement that what the Company has done, to me, seems extraordinary by way of producing information that ought to inform physicians about the importance of pregnancy prevention when they prescribe the drug.

But whether it has been successful or not -- I think the jury is still out. Given the problems with the enrollment to date and the Slone Epidemiology Unit study, I think it is very difficult to know exactly what is occurring among all women being prescribed the drug with regard to their pregnancy exposures and, certainly, with regard to the impact that this program has had on eliminating or moving towards eliminating pregnancy exposures and, finally, towards eliminating birth defects induced by Accutane.

DR. HULKA: Okay, that was a good statement. We again get back to this response rate. Whether it is 28 percent, 50 percent or 53 percent, it is low. We do not know what is happening to all the other women.

I would like to ask representatives of the Company

a question. That is, I would like to know what they consider their best indicators of success of the prevention program and by what time do they think they will have this information? How long is it going to take before you will be able to say, according to your indicators of success, that the program is or is not successful? I wondered if anybody from the Company would respond to that.

DR. ARMSTRONG: I think there are two aspects that would address that. The first is the survey that we do of physicians, both dermatologists and primary care physicians, that assess how often they use the elements in evaluating patients and then how many patients they decide are not appropriate candidates for use. So that would be the first thing. There the indication that we have is that the kit directly contributes to 19 percent of patients that are evaluated with it and not being treated with the drug.

The second aspect of it has to do with the information that will develop out of the Slone epidemiology survey. I think the there the questions that are important will need to be addressed about the quality of the data. This is a matter of assessing the representativeness of the data. We do not have those answers yet but the effort is being made to get those answers.

If I could defer to Dr. Mitchell, I might suggest that he would be able to give you a better idea of when to

expect those kind of data to be available.

DR. MITCHELL: In just the last couple of weeks we sent out about 2000 of the postal follow ups. That rate of send-out is increasing and that is the first wave. So we hope in the next few months to have the initial information from the postal questionnaire. The assessment of representativeness we hope to complete, I would say, over the next three to six months.

DR. HULKA: Would January 1, 1991 be a date?

DR. MITCHELL: Yes, I think that would be reasonable.

DR. HANEY: We have had a lot of focus here on contraception and the people who need the drug, etc. I do believe 93 percent for dermatology prescriptions ought to be 100 percent. I mean I ought not to be using this and I am not sure internists or family physicians, by and large, ought to be doing this. I am curious whether the marketing approach ought to be pretty much restricted to dermatologists. Is that unreasonable?

DR. HULKA: Are you making a proposal?

DR. HANEY: No, I am just curious about it.

DR. SCHROETER: Traditionally, the posture of restricting a drug to a certain specialty group has been frowned upon by that specialty group, especially the dermatologists, and other specialty groups. I do not think that

that would ever fly. For the last 20 years that I have been associated with FDA, that has been tried and, except in very, very special cases, it would never work, especially in this particular case where a number of people are using it. I agree with your position but I do not think that it can be legislated into labeling or a proposal.

DR. HANEY: I was really asking the Company for their focus in marketing etc.

DR. POMERANZ: Well, I would guess that the focus is changing because when I was on the Committee before, seven or eight years ago, we heard that about a third of the patients were getting prescriptions from family physicians and primary care physicians. Now it is down to seven percent. So that is an improvement.

DR. HULKA: Unless I hear something to the contrary, I am going to make a brief statement for the record that we believe that the Company has made a very strong, an unusually strong effort to develop information for pregnancy prevention for patients and physicians. I am thinking about our reaction to part one, and that is to inform physicians and patients of the risks.

Is there any argument with that kind of a statement?

(No response)

The Joint Committees of the Dermatology and the Fertility and Maternal Health Drugs Advisory Committee want

to commend the Company for the very strong program that they have developed to inform physicians and patients of the serious risks to the fetus if a woman takes Accutane while pregnant. It is unusual for such a strong program to be developed and presented by a pharmaceutical company.

Information on success, to date, is very limited since the program only went into full effect in May of 1989. But we have been told that by January 1, 1991 the Company will have data on subjects who have not participated. So they will have some information on the generalizability of the results that they have obtained. They will also have indicators of efficacy of the program.

DR. SCHROETER: I would like to add to that comment. I feel very strongly that Hoffmann-La Roche has made a great effort but if the trends of the data that are now being presented from the Slone group and others continue, and they seem to be going in that direction, this effort is not substantial enough to correct behavioral prescribing problems of the dermatologists, nor the outcome of that, which is fetal wastage. I think that that should be added to that document.

DR. HULKA: Do you agree with adding that? I have to admit that I hesitate on that statement because I do not believe I have seen the data that would substantiate that statement. What we actually saw on reported birth defects

was something like three in 1988, or three in 1987, the two most recent years. I cannot find the data to really substantiate what you are saying. We have seen a reduction in prescribing, not as much as we would like for reproductive age women, but I am hesitant to say something that I cannot document with data.

DR. SCHROETER: I have not asked you to substantiate data. I have said that if the current trends, and whatever the data may be, continue, it is not adequate to curb fetal wastage or to change the pattern of prescribing on the part of dermatologists. Whatever data have been presented today, I am saying that trend cannot continue. The trends are there. You see that there is continued high prescribing. That may change, and that will be fine and I will salute it if it occurs. But if the trends continue, I cannot say that the program is adequate and I think that that caveat must be there.

DR. SCHLESSELMAN: To play the role of the devil's advocate here, perhaps one might take the lack of decline in prescriptions for the drug simply to reflect the fact that the drug has been properly prescribed in the past.

DR. DAVIDSON: That is my problem about this denominator that we are dealing with and these assumptions. I am concerned with over-prescribing but I would be much more concerned about preventing defects. If the numbers stayed

the same and we reduced the defects, then that is what I think we primarily ought to be concerned with.

DR. SCHROETER: That is exactly what I was saying. It is a warning that if we continue to have congenital defects and fetal wastage, then we have a problem.

DR. WOODLEY: One problem I have is what is the number of acceptable but always unfortunate birth defects? It seems to me that as long as we have some contraceptive failure, there are always going to be some. I worried a little bit about that when I heard David Graham, of the OEB Office, in his presentation give what the goals were for this Committee.

I worry about this because much of the activity, the reason we are all here and most of this questioning has been derived from this particular Office, the OEB, and the whole question of Accutane. So I am wondering if we are really talking in the same language. Do they have the goal to eliminate by 100 percent birth defects? Is that the goal? Or is the goal 100 percent of fetal exposure? Those are two different things.

I think we would have a possibility of eliminating birth defects if women who took the drug were ready and prepared to have an abortion if they needed it. But I do not think that we are going to have 100 percent fetal exposure eliminated as long as our birth controls are imperfect, no

matter what we use.

I think this raises the issue of abortion, which might be a maneuver by many women who would choose this when they learn that they have fetal exposure while they are on Accutane. I think one question I have, when trying to weight the testimony of various experts, is what are the background biases of that expert in giving that testimony? The question I would have is does the leadership of the OEB -- David Graham and his colleagues -- do they have a publicly stated position on the right of women to choose whether or not to have an abortion? Because I think if they have extreme views on this issue, then maybe they should not be involved in evaluating a drug like Accutane where the likelihood of abortion in patients is higher than the likelihood on other medications by similar patients.

So would the OEB consider a certain number of fetal exposures to Accutane as an unfortunate but an acceptable level or are they truly trying to eliminate all fetal exposure? We need to answer that question and we need to know their public opinion about abortion.

DR. HULKA: I think Dr. Peck will respond to this.

DR. PECK: As I said earlier this afternoon, the presentation that Dr. Graham made represents the Division of Epidemiology and the Office of Epidemiology and Biometrics, and does not necessarily, in all aspects, represent an Agency

point of view.

Nevertheless, many good points raised by Dr. Graham in his presentation were echoed or mentioned by members of the Committee, as well as other presenters. So, as with discussions internally, we expect these same kinds of issues to be discussed in an open advisory committee.

The Agency is concerned about adverse effects of drugs and the malformed children that we are all concerned about is a common focus. That represents, I think, the commonality of our concern around the table and I think it should remain the focus of the discussion relating to these two questions.

DR. DAVIDSON: Madam Chairman, one thing about the defects, I think as a matter of science, and we have not emphasized it, is that to the extent possible the defects should be more specifically characterized in an effort to make sure they are likely due to this drug because there are going to be some background defects in any population of women getting pregnant that may be just fortuitous.

DR. WOODLEY: Did Dr. Peck answer my question because I do not feel as if I totally got the answer to that question?

DR. HULKA: I think he did, Dr. Woodley.

DR. WOODLEY: He did? Could you restate that for me what his answers were?

DR. HULKA: That our interest and our concern and our efforts should be focused on the issue of birth defects.

DR. WOODLEY: Yes, but we are evaluating testimony by people who are doing studies. We need to know the background bias of those people. I do not think it is unfair to ask for that.

DR. HULKA: Dr. Stein?

DR. STEIN: It may be that not all of these additional measures need to be instituted but one of the points that I want to convey at the end is that we need to begin now to explore them, just in case people come back in January, 1991 to report and there still is a problem. I think because there is such a long lag time in instituting some of these additional measures and because there are so many potential pitfalls, legal, logistical, patient confidentiality, moral, ethical, etc., we should at least begin to look at some of these other measures and perhaps institute some of the potentially easier ones, like recall of unused medication, so that no more time is lost, if that is possible.

DR. SCHLESSELMAN: I would like to comment on the matter of whether there are any latent biases in the investigators reporting results. I think what we ought to concentrate on is the evidence that we have before us. That is out for everyone to evaluate. Quite frankly, I do not know that we need to know any personal position held by an

investigator on such a matter if we have the data presented before us and that is open to public challenge. We might disagree with the conclusions and the interpretation that is placed on those data. But, as long as we have the data before us, we have the opportunity to question their validity and to establish their validity and work on that basis.

DR. WOODLEY: I agree with you. It is the conclusions and extrapolations that I think are the question. I think it is interesting that in the Medicaid studies, for example, in this entire time of the two years that I have been on this Committee, we have never found out whether those women were on other potential teratogens in addition to Accutane. That whole question has not really been explored, or going from interview data to chart records in a physician's office. I think all of those kinds of objective data where we follow up on things are so much more important and I am sort of shocked that that has not been done. Then the conclusions are extrapolated from very small observations.

DR. HULKA: I believe we have worked with the first question and we made the point about the effort that the Company has made but we have also heard the point that if trends continue, they really are not satisfactory. So more effort is going to have to be made.

In part two, question two is really the issue of the additional measures. We started out with the additional

measures and I mentioned several previously, which were in the area of emphasizing things, like the initial pregnancy test; getting rid of residual drug; and a variety of other things.

Are there other points, are there other areas of recommendations that you would like to make? We have heard of this idea of trying to not allow actual prescribing at the pharmacy until certain prerequisites have been met, and have that information either on a consent form or on the prescription form. I have sensed that there was not too much enthusiasm, at least by part of the group, for that. There is concern over the legal aspects, perhaps the coercive aspects and the invasion of privacy aspect. But we can have further recommendations of what you would want the Company to do.

(No response)

It is a very quiet room. Are you satisfied then? The areas where the Committee felt that additional measures must be undertaken are:

- to emphasize an initial pregnancy test and to make sure that the pregnancy test is negative before starting Accutane;

- to develop mechanisms to get rid of the residual drugs and, therefore, the use of Accutane later on when the woman may not be so careful about contraception;

- to emphasize the informed consent and particularly improve non-verbal or non-written forms of information about the need for contraception. This might include video information and the potential for different languages, other than English;

- then to further encourage referral to gynecologists, family planning clinics, family physicians, others who work regularly in providing advice about contraception to women.

DR. SCHROETER: There is an additional one that I think we discussed and there was some consensus. Maybe there is less consensus than I think but I think the new position of the American Academy of Dermatology on the patient information consent form to include consent of the physician and the patient and for the patient to be required to be involved in a surveillance study is very, very important. I think that this should be included in the recommendations of this Committee. If that is not the consensus, then I think people should speak up about it.

DR. HULKA: As I understand it, the change that you are recommending from what already exists is that the consent form would be signed by the patient and the physician and then a copy is sent to Hoffmann-La Roche. State it for the record, please.

DR. SCHROETER: A statement was made, and I will

read it as given by the American Academy of Dermatology task force on Accutane that was presented by Dr. Pochi: That the patient information consent form that is in the drug manufacturer's pregnancy prevention program kit be changed to require, not only that the patient and physician complete the form, but that the patient also be required to enroll in their surveillance program.

Obviously, there are many details that this requires between the lines of the physician, the patient and the sponsor of the drug. But I think that the general consensus and the thrust of this is a positive one to give more responsibility on the part of the physician to involve the patient in surveillance.

DR. WOODLEY: Does that mean that you would not give the drug and you would withhold the drug if the patient did not want to be in the surveillance? I would question whether that is ethical to do.

DR. ROY: That is coercive. I would not agree with that at all.

DR. POMERANZ: I would like to say that I strongly agree with it. Maybe some coercion is needed here.

DR. HULKA: This is the issue, that the physician and patient sign. If the patient does not sign indicating her willingness to be in this surveillance program, the implication would be then that she would not receive the

drug. All those who are in favor of that recommendation, will you raise your hand?

DR. SCHROETER: I do not think we should vote on this. The FDA asked for a consensus of opinion and for a general discussion, and that is what should be done.

DR. HULKA: All right, let's go around the table --

(Laughter)

-- we will not have a general vote on it but would each person state whether you would want such a form signed. What it really means is obligatory surveillance and that each woman really, in order to get her drug now, has to agree to be in this surveillance program. Do you agree or disagree? Let's just be quick; let's not have discussion, just yes or no.

DR. WENTZ: If this were a drug company study, yes. Since it is patient care, impossible.

DR. HULKA: So is that a no?

DR. WENTZ: That is a no.

DR. SCHLESSELMAN: No.

DR. ROY: No.

DR. NIEBYL: No.

DR. MCKAY: No.

DR. HANEY: No.

DR. BARBO: No.

DR. SCHROETER: You have my opinion already.

DR. HULKA: We have a yes.

DR. ABEL: No.

DR. FLEISS: Yes, mandatory on the physician; no, for the patient.

DR. POMERANZ: Yes.

DR. STEIN: I will agree with Dr. Fleiss' position on that.

DR. TSCHEN: No.

DR. WOODLEY: I am glad I am being polled and am not voting. I will say no.

(Laughter)

DR. SCHROETER: I think to try to do a straw vote without considerable discussion of the document or the question at hand, without formal parliamentary procedure, is ridiculous. I do like Dr. Fleiss' amendment to this and that is the sort of discussion that needs to go into something that is as serious as this particular decision or recommendation, I should say, to the FDA and to Hoffmann-La Roche.

I think the consideration of requiring a patient to sign the consent form before they receive the drug is an incursion on their right and I did not comment on that. I like the comment and the suggestion that it is obligatory on the part of the physician. There may be an entanglement of lines of the rights of the patient but I can tell you that third-party payers now require a patient to give data. I see

no reason why we cannot do it for something as serious as this particular type of situation. I think that that needs to be discussed.

DR. TSCHEN: Well, I think we all have the right to make mistakes but that does not make them right. We would like to keep that right.

DR. HULKA: Since we really are running out of time and, admittedly, with as much as has gone on in one day, we are not going to be able to resolve all these issues fully but just really bring ideas to the attention of the FDA and to the Company, are there other serious recommendations that you want to make now as a final statement, beyond what has already been made?

(No response)

It seems then that we do not have any other recommendations that we feel we can make or that are appropriate to make at this time of the day. So we will close this meeting.

(Whereupon, at 5:10 p.m., the Joint Committees adjourned.)

C-E-R-T-F-I-C-A-T-E

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