FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUGS EVALUATION AND RESEARCH

DERMATOLOGIC DRUGS ADVISORY COMMITTEE

OPEN SESSION

Conference Rooms D & E

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AGENDA

OPEN PUBLIC HEARING

OPEN COMMITTEE DISCUSSION

1:15 p.m. to 4 p.m. CLOSED SESSION:

The committee will review and discuss trade secret or confidential information relevant to IND 29-951 and NDA 9-795.

P R O C E E D I N G S

DR. PENNEYS: This is the meeting of the Dermatologic Drugs Advisory Committee. I'd like to call the meeting to order at this time. I would like to welcome all members and guests to the meeting. We'll begin with the open public hearing. I would like to limit presentations to five minutes for each individual. Please, we have a number of speakers.

The first speaker is Dr. Richard Miller from the Teratology Society. Well, if Dr. Miller is not here, we'll go to the next speaker Diane Nygaard, Chairperson, Association of Trial Lawyers of America for Accutane Litigation Group.

MS. NYGAARD: We're going to be showing a videotape. Is there someone here that can assist with the video equipment? My name is Diane Nygaard. I'm an attorney in Kansas City, and I'm also the chairperson of the Accutane Litigation Group of the Association of Trial Lawyers of America. We are a group of attorneys who represent children who have birth defects due to their mother's use of the drug Accutane during their pregnancy.

I am going to show you today videotapes of some of these children. This child is 2 years and 4 months old. He's from the State of New Jersey. His counsel, Mr. Eric Lentz is very kindly furnished us this videotape made yesterday of the child who is present today with his parents.

As you can the child is not able to walk or to talk, and you can see the distinctive ear formation which is unfortunately a characteristic of many of these children.

[Videotape played.]

MS. NYGAARD: This child's mother took Accutane only a few days during the early stages of her pregnancy. The child has very little hearing and poor motor control and of course has developmentally delayed.

The second tape is an older child. This child is 3-1/2 years old, but functioning at a level of probably a 4 to 8 month old and is not able to walk, is not able to talk, and has some of the characteristic facial features of these Accutane children. And again this is not a child that I represent. The tape is furnished by counsel.

On behalf of the attorneys who represent these children, of course, were vitally interested in the work of this committee and it seemed to us that last year from watching and listening to the deliberations that the deliberations focused largely on the data and the statistics. And so we think that the debate should focus where it belongs, which is on these children, and that's why we wanted to have you see just a sampling of two of the many children that we represent with these profound injuries. Thank you.

DR. PENNEYS: Thank you. The next speaker is James Hansen, Chairman, Division of Medical Genetics, College of

Medicine, University of Iowa, who is representing the March of Dimes.

DR. HANSEN: Thank you. I'm Dr. James Hansen. I'm Director of the Division of Medical Genetics and Professor of Pediatrics at the University of Iowa. I'm appearing here today on behalf of the March of Dimes Birth Defects Foundation. It is now a year since I and many other concerned medical scientists testified that Accutane and related compounds can have devastating consequences for the developing baby. The data are irrefutable. The risk is real and the threat continues. The magnitude of the risk for such severe outcomes is sufficiently high to make use during pregnancy absolutely complicated from the standpoint of fetal welfare. These are preventable, serious birth defects.

Despite current stringent warnings regarding the use of Accutane in women pregnant or likely to be, pregnancies are still occurring with severe consequences to the fetus. Sufficient, effective, regulatory steps have not yet been taken. Whereas it is clear that Accutane and related compounds are useful in selected clinical circumstances, it is not clear that these agents need to be distributed in a relatively uncontrolled fashion to meet current clinical indications.

The unrestrictive availability of this and related medications virtually assures some excess continuing level of

fetal exposure. Such an approach will inevitably frustrate, even intense efforts to education health care providers and the general public regarding the hazards of these drugs, and will profoundly impair the attempts at surveillance.

If the FDA concludes that there continues to be a compelling reason for permitting this drug to be prescribed for certain female patients for whom there is no other safe and effective therapy, the March of Dimes Birth Defects Foundation strongly urges that the drug be available only through a highly controlled system, thus precluding general or indiscriminate use.

A recent personal vignette may illustrate some of the current problems. Three months ago, I presented a lecture on birth defects and teratogenic hazards to our freshman medical class. At the conclusion of the lecture, I was approached by a young woman medical student who told me that Accutane had recently been prescribed for her 16-year old sister by her family physician. The description of her sister's skin eruption clearly did not meet the rigorous standards of diagnosis and treatment recommended by many experts. Furthermore the medical student informed me that neither her sister nor her parents had received any information regarding the consequences of this medication, should a pregnancy ensue. When asked whether or not her sister were using an effective form of contraception, the medical student

expressed surprise at my question, and said, she's only 16. I'm sure she's not sexually active.

The marked disparity between the numbers of prescriptions and dosages of Accutane marketed and estimates of the number of patients with severe cystic acne suggest to me that such cases may not be rare. If there ever was a medication targeted to a young population, this one must qualify. How often must we be reminded that adolescents are notorious for the lack of effective knowledge and timely use of contraception. Furthermore, cultural and religious barriers clearly exist for substantial segments of our population which increased the likelihood of pregnancy for both adolescents and other groups of women of reproductive age.

These are substantial problem which can hardly be changed by the short-term limited efforts heretofore proposed. The March of Dimes concludes that there should be a limited number of centers and specialists permitted to prescribe these drugs, a meticulous program of screening, support and follow-up services for treated patients must be mandatory and a method of ensuring informed consent should be provided.

Furthermore, if there is any general message to be learned from this whole painful process, it is that the Food and Drug Administration needs to develop within its committee structure specific panels composed of specialists knowledge-

able in teratology, genetics, epidemiology and related disciplines who will have the authority and responsibility to review potentially hazards agents to which women may be exposed during pregnancy prior to approval for marketing. The present process is insufficient and may inappropriately and inadvertently emphasize the interests of mothers and their treating physicians to the disadvantage of the baby.

In summary, as a physician frequently called upon to counsel and evaluate families in which teratogenic exposure have occurred and on behalf of the March of Dimes Birth Defects Foundation, I strongly urge that the Food and Drug Administration and this panel use its authority and mechanisms to establish a process which will continue the availability of Accutane and related compounds for populations of patients whose disorder clearly warrants this therapy while concurrently minimizing the devastating risk to the fetus, stemming from inadvertent exposure of pregnant women, especially adolescents. Thank you for your time and attention.

DR. PENNEYS: Thank you, Dr. Hansen. The next speaker is Ms. Cathy McGinley representative of the Association for Retarded Citizens of the United States.

MS. BERKOWITZ: Thank you and good morning. I'm Annie Joe Berkowitz representing the ARCUS in Cathy's absence and I serve as vice chairperson of the Legislative Affairs

Committee for the Association for Retarded Citizens in Maryland. I'm also parent of a mentally retarded daughter.

I'm not going to give you all the background that we've outlined in our testimony because you'll be hearing later, I understand, from Dr. Lammer, and we were citing some of his research and the basis on which we have placed much of the emphasis about which we feel so strongly of the damage that can be caused to the fetus when Accutane is prescribed.

I will for the sake of time focus on our recommendations and conclusions. Warning information provided by Hoffman-LaRoche in a letter to physicians dated in September 1988, the company's advice to physicians and the produce information enclosure provided with the drug itself states:

"Accutane must not be used by females who are pregnant or who may become pregnant while undergoing treatment. There's an extremely high risk that a deformed infant will result if pregnancy occurs while taking Accutane in any amount, even for short periods. Potentially all exposed fetuses can be effected."

Major fetal abnormalities related to Accutane administration have been documented and you will be hearing more about those in later medical presentations. There's also an increased risk of spontaneous abortion. Clearly, there is a problem with the use of Accutane in women who are or who may become pregnant.

However, as indicated, Hoffman-LaRoche, has attempted to respond to this problem. Must has been done, but from the perspective of ARC-United States, there is still more work ahead. Hoffman-LaRoche has also included a symbol that is designed to represent the statement, avoid pregnancy. This symbol is featured on the blister-pack on the prevention for pregnancy program kit and on the patient information and consent form, and on the product information enclosure provided with the drug itself.

Hoffman-LaRoche must continue to build on the foundation which they have developed. Efforts must be taken to ensure that there program of Accutane education is not only institutionalized into the policy of the company, but that it is also frequently repeated and that its availability is broadened. This type of educational program must not only be available to those within the medical professional. Any program of prevention education should be available as well to those individuals who may be considered at risk. All available resources, including private and public groups concerned with developmental disabilities and the prevention of developmental disabilities should be utilized to educate the public and the private sector.

The ARC has historically and continues to call for the restricted distribution of Accutane. The Center for Disease Control has issued a restricted distribution scheme

for Accutane that suggests the minimum features that this type of program must have.

These minimum features include such procedures as the availability of the drug through a limited number of centers, review at these centers of patient specific need for the drug, physician and patient education and Accutane risk, and on effective contraception methods, center oversight of effective contraception, monthly not daily dispensing of Accutane, monthly pregnancy tests, center based follow-up and counseling for pregnant women, and a national registry of exposed pregnancies with a pregnancy outcome follow-up.

The availability of this drug must be restricted in order to assure its safest, possible use. Birth defects associated with Accutane must be reduced, if not eliminated all together. We have seen the start of a cautious dispensing of this drug and efforts to educate the public about it, but there remains a very high incidence of birth defects.

The teratogenic properties of the drug are clearly recognized. The Federal Drug Administration should take this recommended Center for Disease Control plan into active consideration and mandate action that includes such features as consideration of those who do not have reasonable access to a center based program. Again, the implementation of these restrictions should be coupled with the requirement of continued and expanded education and prevention efforts by

Hoffman-LaRoche, public and private agencies and the Government. It is time for the Federal Drug Adminstration to move in this area.

The restricted availability of the drug, the ongoing center broad involvement, and the use of effective outreach and prevention education is more apt to lead to a consistent and hopefully successful prevention program. As suggested earlier, it is our position that the birth of any child with an avoidable birth defect must not occur. The ARC is dedicated to the prevention of birth defects and to the prevention of mental retardation. Prevention education and training programs have the potential to decrease the number of children born with developmental disabilities. Thank you.

By the way the copies of my testimony did not arrive by messengers. They were supposed to. I'll be happy to provide copies to anyone who might request them.

DR. PENNEYS: Thank you very much. The next speaker is Dr. Sidney Hurwitz, who is clinical professor of Pediatrics and Dermatology at the Yale School of Medicine.

DR. HURWITZ: Thank you. Good morning. As you heard, I'm Dr. Sidney Hurwitz. I'm clinical professor of Pediatrics and Dermatology at the Yale University School of Medicine. In addition to this, I am a board certified pediatrician. I'm a board dermatologist. I am a founding member and a previous president of the Society for Pediatric

Dermatology in the United States, a founding member and charter member of the side of pediatric dermatology of the international group. I am also the chairman of the section of dermatology of the American Academy of Pediatrics.

Before becoming a dermatologist, I was a pediatrician who enjoyed the largest practice, the largest private solar practice in pediatrics in the State of Connecticut for approximately 15 years. After 15 years, I chose to leave that practice and pursue a residency in dermatology, not because I didn't enjoy pediatrics, but because I had a primary motivation, a primary factor behind my leaving, and that a disease called acne.

I was frustrated for many years as a pediatrician to hear physicians to say acne is not a severe disease; it's merely cosmetic; don't worry about it, you will outgrow it. I watched patients suffer physically and psychologically and I found many patients who were far more scared internally than they were externally. To ignore these individuals with a disease which can scar their lives was totally incomprehensible for me. I went back, I took a residency in dermatology. I worked with dermatology and acne. I have seen over 28,000 patients with acne, some with the most severe forms. I have treated over 450 patients with Accutane.

For some of these patients, it's the only thing that we can use to help them; all the other things did not

work. With this young man we couldn't wait for September, the year it came out, to start him on it, and within four months he was completely cleared. This man I injected practically every week with systemic steroids, drained his cysts. He came back week after week with all the powerful antibiotics and topical medications available until Accutane came along, he was unable to be cured or controlled.

Today the scars that we see on the surface are only superficial. The scars that are internal are the ones that we are concerned most grievously about. This is a scar of a young woman who tried to commit suicide because she could not face the world with a disease called acne.

This young woman refused to get out of bed in the morning, refused to get a job. She was a beautiful young woman who said Dr. Hurwitz, if you can get me under control, I would do anything. Within a few short months, she was completely clear, happily married, and on her way to living a normal life again.

This young man, Bill, when they came to see me said, Dr. Hurwitz, I've had this disease for so many years, nobody can help me. How long do I have to live with this. When he started to cry, I walked out of the room to regain my composure before I could go back in and talk to him. I said, Bill, give me a few months, and we'll get you under control. This is Bill a few months afterward. Happy as a lark, also

married, leading a nice, happy life.

But what can we do with these with severe acne, severe pustular cystic lesions. This young man used to drive down from Massachusetts with severe pustular cystic lesions on his back that were draining. He couldn't sit in the car. He couldn't make love to his wife. He would have to see a surgeon and have these drained. Everything we did was to no avail until Accutane came along and changed his life.

This young man ended up in a psychiatric institution. He is now under control. He's going to school, and he looks great, thanks to Accutane. This is the young man that I showed you before who's now a law student, using no medications and able to live a nice, happy healthy life.

I too am concerned about the devastating effects of malformations. I am concerned. I am a concerned physician. I am not happy about what I have heard about malformations. This cute little child does not have Accutane syndrome; he has the fetal hydantoin syndrome. Probably one of the most devastating syndromes we see of fetal malformation. It affects two our of every 1,000 individuals who are pregnant when they are taken an anti-convulsant treatment.

I ran through some statistics on Friday. I called Kenneth Lyon Jones whose the author of Smith's Malformations, Recognition of Human Malformations. I called Harvard and spoke with Lou Holmes who's done studies on fetal malforma-

tions. I took the figures they gave me and put this on a national basis and came up with thousands of children with fetal hydantoin syndrome. Up to 3,000 a year perhaps with major malformations, including cardiac malformations, tetralogy flow, septal defects, ambiguous genitalia, genital urinary malformations. And another 9,000 that probably don't show their manifestations for years later, when they are mentally deficient or developmentally deficient.

Does this mean that we take this valuable anti-convulsant drug off the market too? How can we, as physicians and individuals ignore the benefit for patients who need this drug, the only drug we have available. We have to monitor it. We have to leave it available. We have to monitor it properly. For us to deny this drug to people who require it, acne is not just skin deep. This would be unconscionable. Thank you very much.

DR. PENNEYS: Thank you, Dr. Hurwitz. The next speaker is Dr. Mary Spraker from Emery University who's speaking for the Task Force of Pediatric Dermatology.

DR. SPRAKER: Good morning. I speak to you today as a concerned pediatrician and dermatologist and practicing pediatric dermatologist, active member for the Society of Pediatric Dermatology, and a mother of an eight-month baby boy, named Henry. I'm also the current chairman of the Academy of Dermatology's Task Force on Pediatric Dermatology.

Though in this forum I can only speak to you as an individual.

Because of my dual career in both pediatrics an dermatology, I like Dr. Hurwitz feel, I understand the issues as they pertain to both and infant and to the patient with acne. To remove Accutane from the market would be a crime against patients with severe acne which belittles the suffering caused by their disease. Acne is not a lethal disease, but does profoundly effect lives.

All of us remember patients, acquaintances, personal friends who suffered from this disease. My example is a girl in my high school class that played the flute. She was bright, could have been pretty, had severe acne. Because of the acne she hid behind her glasses, had few friends, and is scared to this day. I remember my mother talking about the treatment that was attempted and was unsuccessful, antibiotics, restrictive diet. She even received X-radiation therapy.

We no longer see many young people like this anymore. We used to see them on the streets and on the buses. We don't see them any longer because of the miraculous effect that Accutane has on such patients. In one month the patient looks better. By the end of the standard 16 to 20-week course of therapy, 90 percent of patients are clear and even their scarring tends to improve as it remodels. Even more wonderful, most patients remain in remission when

therapy is discontinued. There is no patient more gratifying to treat.

It was known at the time the drug was first introduced that it was a potent teratogen in animals that was not supposed to be used during pregnancy. This was emphasized to all of us 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 national meetings which are attended by approximately 80 percent of all practicing dermatologists, there was great discussion about what could be done to prevent these pregnancies.

This is a terrible ethical dilemma for me as a dermatologist or as a pediatric dermatologist. What can I do to make sure that none of my female patients become pregnant? I certainly warn my patient. I repeat the warning at follow-up visits. I emphasize the need for adequate contraception. Is it ethical for me to insist she take, for example, contraceptives, even if she insists her current contraceptive method is adequate? This is especially difficult for me because there are complications from contraceptives. Occasional patients die from oral contraceptives, and they're not full proof, even the best contraceptive.

Isn't it the patients right to participate in this decision? Ironically, Accutane is perhaps the opposite of a

contraceptive. Suddenly a young woman who has, whose acne has made her physically unattractive, blossoms. She looks great. She feels great. Suddenly she's attractive to the opposite sex.

All drugs have side effects, including lethal side effects. Penicillin and antibiotics kill. Yet there's no talk of taking antibiotics off the market or limiting their use to life threatening diseases like meningitis or pneumonia, not to treat less serious infections like strep pharyngitis or ear infections which aren't fatal usually, but due cause pain and permanent deformity. Many other drugs damage the fetus, dilantin, alcohol. Vitamin A is damaging to the developing fetus, but is available over the counter.

The suggestion that Accutane usage be decreased by 20 percent is both arbitrary and impractical. The drug has never been approved for mild acne. So which of my severely involved patients do I not treat? What do I tell this patient? The regional center ideas are impractical. There are too many patients who would need to travel too far, too often. And this doesn't seem to solve the problem anyway.

During the clinical trials of the drug in a controlled IND setting, there were five pregnancies in 100 women. Never in the history of drug prescribing has more been done to educate physicians and patients regarding the teratogenicity of the medication. The paperwork my patients

and I now need to fill out to prove she is informed is incredible, time consuming, worthwhile, I believe in this endeavor, but this is the best answer I can suggest to help solve our current dilemma.

As physicians we can guide our patients, but we are not god's who have the power to completely control them. We should respect the fact that our patients must take some responsibility for their disease and the treatment of their disease. The questions we raise today are not black and white. There may not be a perfect answer. We must be well reasoned and wise for what we decide will have important ramifications regarding many other medications, both old and new. Thank you.

DR. PENNEYS: Thank you, Dr. Spraker. The next speaker is Marty Fritz who is an attorney from Honolulu. Is Marty Fritz in attendance? Are there any other speakers for this portion of the agenda? Has Richard Miller arrived?

Well, if there are no other speakers, then I will move on to the next agenda item which is the open committee discussion. The first speaker will be Dr. Carl Peck who is Director of the Center for Drug's Evaluation Research. Dr. Peck?

DR. PECK: Thank you, Dr. Penneys. I'd like to take a couple of moments and address the committee. I'd like to tell you a little bit about our center and especially what

is new. First of all I'd like to welcome you to this particular advisory committee meeting. I'm told that the committee first met in 1971 and that it has met at least once a year in the meantime and often twice a year. So this must be between the 20th and the 40th meeting of this committee.

I'd like to especially welcome two new members, first of all Dr. Jaime Tschen. Would you like to stand up for a moment. Dr. Tschen is associate professor, Department of Dermatology at Baylor University College, University of Medicine. And Dr. Arnold Schroeter--Dr. Schroeter is professor and chairman of the Department of Dermatology at Wright State University, School of Medicine in Dayton, Ohio. We welcome you to the committee. We know you'll have a stimulating time, and we hope you'll have a satisfying time during the next three years.

I'd like to also acknowledge with gratitude and with sadness the pending retirement of three members of our committee. First of all, our chairman, Dr. Neal Penneys who is professor, Department of Dermatology at University of Miami, will be retiring from the committee on the 31th of August; Dr. Lynn Drake who is deputy director of the Department of Dermatology at Massachusetts General Hospital; and Dr. Shirley Osterhout who is not here today. All three will be retiring on 31st of August, and we're very grateful the loyal and energetic contributions that you've made to this

committee.

You should know that I personally and the commissioner and all the staff of the center consider the advisory committee system to be an integral part of our activities at the center. And that's why I want to take some time this morning to tell you a little bit about the center that you may or may not know and to update you on some new developments.

You probably know already that of the 7,000 employees at the FDA, we number almost 1,200. We're one of five centers, and this is the somewhat complex organizational chart of the center. You can see by scanning the overall functions of the center that we have our fingers in a number of pies that emanate from our responsibilities into the Food and Drug Act and its various amendments. For example, as you'll hear later today, we're deeply involved in post-marketing surveillance of marketed drugs. Dr. Jerry Fleiss heads a group of over 100 epidemiologist and biostatisticians that review the experience with drugs once they're marketed and provide consulting services for the rest of the center in the areas of biostatistics and epidemiology.

We have an active linkage with our field laboratories and field offices and investigative resources within the agency to inspect drug manufacturers, to ensure quality of manufacturers, and importantly to inspect and investigate the

integrity of the clinical investigation resources that feed data into new drug applications. The heart of the new drug review is located in two sections here, the Office of Drug Evaluation I, headed by Dr. Bog Temple and the Office of Drug Evaluation II, headed by Dr. Jim Bilstad.

This used to be one drug evaluation section, but in about October of 1987, it was split into two. Shortly before that a new division had sprung up in the office that was the Division of GI and Coagulation Drug Products under Dr. Steve Fred. In the meantime, some other changes have occurred and I'd like to tell you a little bit about them.

In March of '88, we split out the anti-virals drug product review group from the Division of Anti-Infectives Drug Products and made that a separate division. That was done in order to be able to handle expeditiously the exponentially growing number of INDs and some NDAs for anti-viral drug products, especially those against HIV agents. Dr. Alan Cooper heads this group. It has grown from roughly 15 at the time of its inception to now almost 40 and because we're seeing more than a doubling of applications each year, we're expecting that section to double again in the next year.

I'll have more to say about the Anti-Infectives Division which you're apart of in just a moment, but let me tell you a little bit about some new starts in the Office of Drug Evaluation I. We have reconfigured some drug evaluation

groups and pulled together the oncology and pulmonary group and asked Dr. Greg Burke to become the acting division director for that section. Dr. Burke is a highly respected bright young oncologist who's been at the FDA for a number of years, and we expect to be able to give added emphasis to the important drug development programs across the country and at the NCI in drugs for cancer and to develop the pulmonary drug review group more fully.

Dr. John Palmer has taken on a reconfigured section here, radiopharmaceutical and surgical dental, and here we expect to provide some new regulatory developments to handle the innovative PEP, NMR and other technologies that are rapidly entering the nuclear medicine community.

We put several product areas together into a special new section which we're calling a pilot review staff which reports directly to me. This will include the anti-inflammatory, anesthesiology, and analgesic drug products. We asked Dr. John Harter to act as the director of this unit, and I will become much more intimately involved in the review process with these products.

The spirit of this most recent reconfiguration is multi-factorial. We wanted to provide an opportunity for new leadership, and Dr. Burke and Dr. Harter to develop skills and try out new ideas. An important additional objective was to enable the implementation, particularly in this group

of a number of innovative ideas for drug review. You may have heard last year, Dr. Harter initiated a way of compressing the tertiary drug review time into a single day followed by a couple of weeks of final tying up of loose ends in the so-called NDA day.

The NDA day is an initiative to bring together all of the reviews from within the center that comprise the review of a new drug application, along with the office director to make that review essentially brought to a point of intensity in one day, followed then by final negotiations in the weeks that follow.

I'd like to spend a moment to tell you a little bit about what's happening in the Division of Anti-Infective Drug Products. Dr. Ed Taber who was the permanent division director left last summer to take a senior position at the National Cancer Institute. Dr. Lillian Gavrilovich has graciously and with great excellence taken on the acting directorship of this division, and has done a very excellent job in that. We initiated a search last summer for candidates for the permanent position, and I'm happy to say that we have narrowed it down to a short list, and we expect within the next several months to come to closure on identifying a new division director for this division. We would expect at the next meeting to have the presence of a new division director.

I'd like to also tell you for a moment a little bit

about another new element within the center which we call the professional development staff. With an organization this large with a need for highly specialized talent in the area of drug review and drug development, we have an important obligation to continue to attract good reviewers and to maintain their skills. We've established within this staff office a recruitment resource which provides professional recruiting resources for the attraction and interviewing and final selection of medical officers and eventually other officers for the center.

Perhaps even more importantly, this group has developed a staff college which has the objective of providing a variety of training programs for new and veteran reviewers within the staff to bring their skills in a variety of areas that are important for evaluation of INDs and NDAs up to speed as soon as possible. For example, they can take courses in basic statistics, various advanced statistics, topics of pharmacokinetics, food and drug law, clinical trial design and analysis and other such matters.

In addition, this group has established several joint training programs with local universities. It drew upon the already well established training program that the Division of Anti-Infectives had in place with Children's Hospital. For several years now, that division has had a joint training program in pediatric infectious diseases and

regulatory science with Children's Hospital. We now have a joint clinical pharmacology regulatory science fellowship with the Uniform Services University and also with Georgetown University, and we are hoping to develop similar programs with other local universities.

To round out the discussion of the center, the Office of Drug Standards deals with over the counter drugs and generic drug applications, and the Office of Pharmaceutical Research Resources provides a variety of research capabilities so that reviewers on the staff can engage in active research while they're doing review, as well as undertake research projects that answer specific regulatory questions.

I want to end my comments by expressing to you once again how important we feel the advisory committee system is to us. It is so important that the administration of that comprises a staff office that reports directly to me. Mr. Jack Gertsulk heads this division which handles all 17 drug and biologic review advisory committees, 14 of which are in the drugs area. We're very appreciative to the extraordinary job that that staff does in preparing for these meetings and pulling these meetings off.

I'd like to thank Dr. Isaac Roubein, especially for the present meeting, and it's important for you to know that we value very much the independent advice that you give us.

And we're appreciative of the opportunity to bring this group together in a public forum and to hold meetings like we're having today, where we can discuss in an open public forum all of the assets and limitations, the benefits and the drawbacks of each of the drugs that we are considering for marketing or that are already marketed, as in the case today with Accutane. Thank you.

DR. PENNEYS: Thank you, Dr. Peck. Speaking for the retiring members, I'd like to say it's been a most interesting and rewarding experience participating in these meetings. The next speaker will be Dr. Lillian Gavrilovich who is the Acting Director of the Division of Anti-Infectives Drug Products, who has some welcoming comments.

DR. GAVRILOVICH: Thank you, Dr. Penneys. My name is Lillian Gavrilovich, and as Dr. Peck mentioned I'm the Acting Director of the Division of Anti-Infective Drug Products to which dermatology drugs belong to. I will cut my speech short. I don't want to repeat what Dr. Peck said. Again, but I would personally, like Dr. Peck, to thank Chairman, Dr. Penneys, Dr. Drake, and Dr. Osterhout who's not here with us for their work on the advisory committee, and I would like also to welcome two new members, Dr. Tschen and Dr. Arnold Schroeter to the advisory committee. Dr. Schroeter is not really quite new; he's quite familiar with this job.

I would also like to introduce and to thank Dr.

Ridgely Bennett for being here with us. Dr. Bennett is sitting here with us at the end of this table. He's OB/GYN specialist with Endocrine Metabolic, Division of APA. He's kind of a liaison with the Maternal and Child Health Advisory Committee of the FDA to which the Accutane issue is going to be presented next month. Thank you.

DR. PENNEYS: Thank you very much. At this time, I would like to ask Dr. Richard Miller to speak. He was one of our speakers from the open public hearing.

DR. MILLER: Good morning. I'm Richard Miller, professor of Obstetrics and Gynecology and Toxicology at the University of Rochester's School of Medicine and Dentistry. This morning I am representing the Teratology Society. We do most appreciate the opportunity of addressing the committee once again. The Teratology Society is a professional organization of basic scientists, pediatricians, obstetricians, toxicologists, and other health scientists concerned with the etiology and prevention of birth defects, and other aspects of abnormal development.

Members of the Teratology Society are from academia, Government, and private industry. As a professional society, we have been concerned with the teratogenicity and other developmental effects of retinoids. Many, if not most of the studies, demonstrating such effects of retinoids have been conducted by members of the Teratology Society. Our Public

Affairs Committee is preparing statements on isotretinoin, Accutane, and etretinate tegison for publication.

My remarks this morning summarize the recommendations in the Accutane statement. The statements to be given here have been reviewed and approved by the Council and the Public Affairs Committee of the Teratology Society. The Teratology Society believes that the malformations caused by Accutane are preventable. Despite the national publicity concerning the teratogenicity of Accutane, following last year's committee hearing, pregnant women continued to be exposed to Accutane.

Currently we see three obstacles to the prevention of the birth defects caused by Accutane. One, a large number of women in the age range from 12 to 44 continue to be treated with Accutane. All contraceptives, the most efficacious currently approved contraceptive in the United States have typical failure rates of about 3 percent. And third, the lack of routine close monitoring for early pregnancy detection. The manufacturer has estimated that women aged 12 to 44 have received 65,000 new Accutane prescriptions during 1988. This number of prescriptions seem to be well above the published estimates of the incidents for recalcitrant cystic acne.

Your committee may be in a position to assess, if there is over-prescription of Accutane. This number of

users, coupled with the limitations of currently available contraceptive methods in the United States creates a significant problem. Trestle and Cost estimate based on all of the available studies that the typical failure rate of all contraceptives is approximately 3 percent. Other reviews have recently been published by Michele in the New England Journal of Medicine and Grimes in the Journal of the American Academy of Dermatology.

It is not difficult to estimate that several hundred women could become pregnant during the treatment period with Accutane even while using an oral contraceptive. This estimate is based on the estimated number of new prescriptions and a failure rate of approximately 3 percent for oral contraceptives. Injectable progesterone type implants are available outside of the United States and have shown to be very effective in preventing pregnancy. The observed failure rates of injectable progesterone type compounds and implants have been estimated at approximately 0.3 percent, about a 10-fold improvement from oral contraceptives.

If all fertile female patients using Accutane would also use an injectable progestin or an implant instead of oral contraceptives, this could reduce pregnancy rates resulting from contraceptive failures by about 90 percent. The recent recommendations of another advisory committee to

the FDA to approve implants in the United States is a step in the right direction. Until such products are available, the use of multiple contraceptive methods should be continued.

Recommending the concurrent use of barrier methods with oral contraceptives may be an important behavioral modification as well. The possibility of contraceptive failure underscores the need for pregnancy monitoring. For a drug that carries a category X labeling which means contra-indicated in pregnancy, it would seem logical that the prescribing physician would like to discontinue therapy as soon as contraindication emerges.

Clinically available ultra-sensitive pregnancy tests would detect pregnancy at or shortly before the anticipated missed period. We see two advantages for including repeated early pregnancy detection. First, having to return for a pregnancy test and a new prescription on a monthly basis may provide another behavioral modification about the careful use of contraceptives. Second, those patients that would consider terminating an Accutane exposed pregnancy as suggested in the current labeling would face a simpler and safer procedure than the ones available later in pregnancy.

The Teratology Society supports and encourages the educational programs developed by the manufacturer to make women aware of the risk of Accutane used during pregnancy and

to assist prescribing physicians in the pregnancy prevention program. The Society encourages the FDA and the manufacturer to continue to support efficient and unbiased surveillance of pregnancy exposures among female Accutane users. We believe that any pregnancy occurring to female Accutane users should be considered a failure of the pregnancy prevention program and should be carefully evaluated to determine the reason or reasons for failure and to develop additional strategies to prevent such occurrences.

Therefore, the Teratology Society offers the following recommendations to this committee. the Food and Drug Administration and the manufacturer:

(1) efforts should be made to decrease the number of Accutane prescriptions to fertile females;

(2) the extreme hazard associated with Accutane exposure during pregnancy necessitates that female users be provided with the most effective means of contraception. For example, long acting progesterone type injections or implants, coupled with barrier methods;

(3) monthly pregnancy testing should be performed in fertile female patients, and Accutane prescriptions should only be continued if there is a negative pregnancy test;

(4) an active surveillance of Accutane use among female patients should be continued;

(5) and every occurrence of pregnancy among

Accutane users should be evaluated to determine the reasons for the failure in the pregnancy prevention program;

(6) and to develop additional steps toward preventing such occurrences.

These are interim recommendations with the hope that they will be effective in preventing pregnancies in female patients being treated with Accutane. Your committee should review the surveillance data in a reasonable period of time to determine if these measures have been effective. That is, preventing pregnant women from being exposed to Accutane. If such measures are not effective, this committee will be faced with implementing stronger measures to prevent exposure to Accutane during pregnancy, such as restricted distribution. Thank you very much for your attention.

DR. PENNEYS: Thank you, Dr. Miller. Has Marty Fritz arrived? This is your last chance. If not, our next speaker is Dr. Isaac Roubein who is the secretary for this advisory committee who has a few comments..

MR. ROUBEIN: Based on the information provided by the members of the committee, the agency has taken the following actions to preclude any appearance of a conflict of interest. It has been determined that all interests, inference regulated by the center for drug evaluation research which have been reported by the participating members was no potential for an appearance for a conflict of

interest at this meeting when evaluated against the schedule agenda.

However, in the event that the discussions should somehow involve these firms, all participants are aware of the need to exclude themselves for such participation and their seclusion shall be noted in the record. Thank you.

DR. PENNEYS: Thank you, Dr. Roubein. The next agenda item is the current status of Accutane. Our first speaker is Dr. Colonel Evans who is group leader, who will give some introductory remarks.

DR. EVANS: I'd also like to welcome you this morning. Again, we'd like to indicate our appreciation for our members who are leaving and welcome our new members. Because we have several new members, I would like to take advantage of the opportunity to go through some of the chronology of Accutane, because as you know, no drug with terminological significance has received this much regulation or oversight.

In January of 1982, the Dermatologic Drugs Advisory Committee voted for the approval of Accutane with certain labeling revisions. In April of 1982, the draft labeling was again reviewed by the advisory committee and a half page contraindications, including teratogenic effects were listed. In August '82, a FDA bulletin announced the FDA approval of Accutane and discussed contraindications during pregnancy.

In September of that year, Hoffman-LaRoche introduced Accutane with a teratogenicity warning, based on animal studies. In July of '83, the company sent letters to 500,000 physicians and pharmacists because of the first reported cases of human birth defects.

In November 1983, the Food and Drug Administration in their FDA bulletin, reported major human birth defects and warned against use in pregnancy. In 1984, the company sent letters to physicians and pharmacists on additional clinical and safety information, including a revised patient brochure. In March 1984, there was a FDA press release which announced additional birth defect warnings and alerted blood banks not to accept blood from Accutane users.

In late 1984, the Roche Company made a presentation to the advisory committee updating changes in the package inserts, reporting that at that point there were 20 cases of birth defects. The committee voted to continue to closely monitor the drug. In August '84, a FDA bulletin updated the birth defects reports and discussed latest labeling changes, and in October of that year, Roche sent physicians and pharmacists new clinical and safety information added to package insert and patient brochures.

In late 1984, the Dermatology Advisory Committee was again updated on the adverse events that had taken place. In December 1984, the Roche Company placed advertisements in

the Journal of the American Association and the Archives Dermatology providing guidelines for use in female patients. In August '85, another FDA drug bulletin was distributed to all health professionals on package insert revisions. And in October '85, two articles were published in the New England Journal of Medicine on Roche sponsored studies of birth defects.

In June of '86, Roche mailed to physicians and pharmacists the most recent revisions of the package insert. In February of 1988, the FDA and CDC staffs notified the FDA commissioner of additional cases of Accutane birth defects which brought us up to the meeting of the Dermatology Advisory Committee in April of 1988.

When the committee last met which was last year, we had a document which had been put together by the members of the staff of the Division of Epidemiology and Statistics here in FDA, and based on documentation that they had, they indicated that Accutane was markedly over-prescribed. There were far too many cases of pregnancy exposures and in addition to that, they had accumulated over 60 cases in which children had been born with birth defects due to Accutane.

Based on this kind of information, we asked the Dermatology Advisory Committee whether it was reasonable to remove the product from the market. The response was that it should be continued to be marketed. We also asked them

whether it was reasonable for us to contraindicate Accutane in women of childbearing age. We got a negative reply, but the committee suggested that there be certain other changes regarding the physicians labeling, the patient's labeling and some consideration of some sort of restricted distribution.

What has the FDA done since that time? One of the things that has been done is we've had the formation of the Accutane monitoring group which is an interoffice coordinating body to make sure that things didn't fall between the cracks between the company, FDA and other interested parties. This is headed by Dr. Robert Nelson who also is supervising the AZT monitoring group. As a result of this, we've had quarterly reports form Roche giving us up-to-date information on adverse effects, pregnancy exposures, also drug manufacturing and drug use data, and advertising and educational programs.

In turn we have assisted Roche in the development of certain changes in the labeling and in the development of their pregnancy prevention program. A letter went out from the FDA to Hoffman-LaRoche last summer, and it outlined the actions which we felt should be designed to limit or prevent the misuse of the drug. Among these recommendations were that Accutane must be dispensed in a blister-pack with the patient warnings and other information as part of the package itself. This is in addition to the currently used pamphlets

that physicians and pharmacists are asked to give patients.

It was recommended that there be a photograph showing the severity of the birth defect which will be used on the labeling. It was also recommended that women patients be asked to sign a form acknowledging their understanding of the very great likelihood of serious birth defects if the drug is taken during pregnancy. Regarding the physician labeling, it was recommended that a stronger box warning statement which must have print twice the size as the present label. The statement should affirm that the drug is not to be used for women of childbearing age, unless the physician determines that she meets all the following criteria: one, she has severe disfiguring acne; she can understand and carry out instructions; she is capable of complying with mandatory contraceptive measures; she has received all the written warnings of the hazards of pregnancy and has had a negative pregnancy test within two weeks of initiating therapy. Finally, that the drug's use will not begin until the start of the next normal menstrual period.

A statement should be added to the precaution section to explain the magnitude of the risk in fetal abnormalities. The kinds of birth defects that have been seen and the necessary of pregnancy counseling. Regarding the patient labeling, it is our recommendation that this must detail that there is an extremely high risk that a deformed

infant will result if pregnancy occurs while on Accutane. Materials must include a photograph or a reasonable facsimile of an infant with the characteristic visible external deformities, incurred due to exposure to Accutane, identified with an appropriate caption.

There must be a non-pregnancy symbol on each page of the patient material and on each panel of the blister-pack. There must be an informed consent with large type discussion of fetal abnormalities. In addition, there should be educational initiatives. And the letter calls for extensive educational campaigns aimed at physician, pharmacists, and patients, and encourage publication of advertisements on the teratogenic effects of the drug.

The FDA letter finally stated that the blister-pack should include a tear off prepaid postcard addressed to the Hoffman-LaRoche Company requesting the patient's name, phone number, and permission to be contacted. This is important because FDA hoped that the company would do a follow-up survey to ascertain patient awareness, disease status, contraceptives used, et cetera.

The goals of these activities are to reduce the prescribing of Accutane, and also to eliminate pregnancy exposures, birth defects, and the need for abortions. At this meeting, we have not asked any specific questions of you. We know that it has not been enough time to determine

or assess the effects of the interventions that have taken place.

While we have not asked you specific questions, we will certainly welcome your constructive comments. I would also like you to know that this material in general will be presented to another of FDA's committees, the FDA Committee on Maternal and Child Health, for their comments. I want to thank you for your attendance, and we look forward to a productive meeting. Thank you.

DR. PENNEYS: Thank you, Dr. Evans. I think we should move on to the next presentation by Hoffman-LaRoche.

DR. CUNNINGHAM: Good morning, Mr. Chairman, members of the advisory committee, ladies and gentlemen. I am Dr. William Cunningham and I'm Director of Medical Affairs and Health in Hoffman-LaRoche, the Division of Roche Malacia. I'm also on the attending staff at Columbia Presbyterian Medical Center in New York, where I practice dermatology and teach the medical students and residents, and award certified dermatologist.

We'd like to thank you very much for your invitation to participate in this status update this morning. We feel this has been a very worthwhile exercise for us in the past and we feel that today's meeting is a very positive step to develop the collaborative spirit that we've experienced throughout the years.

Also presenting this morning will be from Roche, Dr. Robert Armstrong who is Director of Clinical Research at Roche Dermatologies, Dr. James LaBraico who is Senior Director in the Department of Drug Safety, Hoffman-LaRoche, and joining us will be Dr. John Strauss who is Professor and Head of the Department of Dermatology at the University of Iowa, and Dr. Allen Mitchell, the Associate Director of the Slone Epidemiology Unit, the School of Public Health at Boston University.

This is my fourth presentation to the advisory committee since 1983. I've been involved with Accutane since 1981. I've attended nearly every meeting since then of Accutane, and I've learned from the discussion, I think we've benefited as a group to participate in this together. This is probably the thorniest issue you've ever faced and certainly the thorniest issue I've ever faced in my life. Our goal is reducing dramatically the number of malformations associated with Accutane.

After this morning's videotape and human experience, I think it's clear that we share your grave concern about the seriousness of the problem that we face. I was also reminded by Dr. Spraker's comments that in my own personal life, the most joyous moment in my life, the birth of my son was also overshadowed in a way by the events of Accutane over the last years in my life when my son was born with no malformations.

I must admit on a personal level, I breathed a real sigh of relief. It's an issue that I'm facing today, since my wife was due on Friday again, and I think that all of you in the room probably share this deep emotional impact that we have in this issue.

In response to the challenge of last year, in April we implemented in October, a massive effort called the pregnancy prevention program. We discussed this with the committee in April last and after many many suggestions, we tried to incorporate as many of the steps that were deemed practical and desirable in the program, we as Dr. Evans has mentioned, agreed with the FDA at various meetings throughout the summer and fall of last year on the entire aspect of the program and the program was introduced in October of 1988.

The pregnancy prevention kit has been, I think, in the office of the dermatologist, a great success in general. Last week we lost the blister-pack, after a few technical delays that prevented us from launching it a bit early, but I think you'll hear this morning that the scope of that effort is quite significant. We agree with Dr. Evans that the full impact of the program will be felt in the ensuing months.

Today's agenda will begin with Dr. Strauss introducing the medical role of Accutane and the therapeutic armamentarian. This is truly a unique drug. It's a curative drug in many instances. No drug was available for treatment of

this severe disease in the past, and this is truly a medical breakthrough.

Dr. Armstrong will review the status of pregnancy prevention program. I will outline some of the epidemiology of the usage of the drug. In this regard, I would say that we share Dr. Evans' concern about the usage. We've seen a study downward trend in the usage of the drug over the years, and I'll give you more specifics on that later. There's a clear reduction, as well in the number of malformations over the years, and we find that a very positive sign that the events of 1983 and '84 and the events of 1988 have had an impact where it counts, that is, in reducing human malformations.

Dr. James LaBraico will discuss the actual data regarding pregnancy and malformation with you. And then, Dr. Allen Mitchell will discuss the extensive follow-up survey which we've planned and implemented in January. Dr. Strauss?

DR. STRAUSS: Thank you. Mr. Chairman, members of the advisory group. For those of you who are not dermatologists, I would like to first list my qualifications. I'm a past president of the American Academy of Dermatology, the Society for Investigative Dermatology, and the Council of Medical Specialty Societies. I still serve on an chair several committees of the American Academy of Dermatology and my current administrative responsibilities, include service

as the secretary of the American Dermatological Association, Director of the American Board of Dermatology, and a member of the Advisory Council of the National Institutes of Arthritis, Muscular Skeletal and Skin Diseases. In between all these, I serve as Professor and Head of the Department of Dermatology, University of Iowa, the post I've held for 11 years.

Throughout my many years of professional career, my main and continuing research interests have been related to the pathogenesis and treatment of acne. I've been involved in the use of Accutane since 1978 when I became the second investigator in the United States to use this drug for acne. I think there's no question that I am recognized as a worldwide authority on acne.

I appear before your Committee under the auspices of Hoffman-LaRoche, but I want to emphasize that I am not under a retainer nor do I serve as a formal consultant to the company, although I obviously have close relationships with them because of my research interests and I do serve on a fee-for-service basis from time to time. I personally requested that they allocate time to me before I had the knowledge that the American Academy of Dermatology would be here. My remarks could easily be given as a representative of the American Academy of Dermatology, and I did serve as a representative of the American Academy of Dermatology to the

Task Force on Accutane of the American Academy of Pediatrics.

I appear here because of my keen interest and concern for patients with acne and most importantly for those who suffer the devastating consequences of severe nodular cystic acne. At the same time, I share with all the previous speakers a great concern about the birth defects and their prevention. Accutane has had a tremendous impact on the management of these severe cases of acne, and it is fair to state that in all my years in dermatology, I know of no drug which has had a comparable impact.

It is now possible to treat a segment of the acne population of previously were untreatable with any modality that we had, be it high dose antibiotics, dapsone, high dose estrogens, corticosteroids, and many other agents that have been used in the past. I am as concerned as everyone here about preventing birth defects, but at the same time, let us remember that acne is not a benign disease. In the group of patients with severe nodular cystic acne, treatment failure can lead to lifelong scars, as I will demonstrate in the following slides.

A male with very severe acne. Another male with very severe acne, involvement of the back. This certainly is devastating to the individual, but it isn't a disease that is just severe in males. On the next five slides, I will quickly show you severe scarring and severe nodular cystic

acne occurring in female patients. The pictures themselves speak for themselves. These are all women who are tremendously scared, both emotionally and physically by their disease.

And I can show you the consequences of not treating. These are two patients that I saw when I still in Boston many years ago who were told by a physician that they did not have to be treated. The scars that I'm presenting to you in these two patients, and these are scars and not nodular cystic lesions are certainly lifelong and are certainly tremendously damaging.

I want to emphasize that these are examples of patients who were seen prior to the advent of Accutane or for one reason or another did not receive the drug. The physical and livelong psychological impact of the type of scarring that I have shown is tremendous. With adequate dosing, Accutane undoubtedly could have produced, not only remissions, but in close to 90 percent of the cases, these remissions would have occurred with minimal scarring. And the patients would be unlikely to acquire further extensive therapy because of the long lasting remissions.

I want to illustrate the type of patient and the type of clinical response that can be expected, and I'll run through these very quickly because similar pictures have been shown by others. This was one of the first patients I treated in 1978, totally treatment resistant to everything

that had been tried, and everything had been tried. This is how he looked 20 weeks later, and as far as I know he still looks like this, some 11 years later.

Another individual with severe nodular cystic acne with dramatic improvement with one course of drug, and to illustrate once again that this is not a disease restricted to males. Here is a patient, not mine, but Dr. James Ladens who was treated. This is how she looked at the end of treatment, and some one to two years later, essentially clear.

Now I would like to address the question as to who deserves this drug. We don't have true figures on the incidence of nodular cystic acne. The National Health and Nutritional Examination's Survey data is often quoted. I feel that this data is not reliable for the purpose in which it is being used because there were no established criteria for making the diagnosis of nodular cystic acne. My own estimation is that 2 to 5 percent of all women with acne might warrant treatment with the acne at some time.

Considering a birth rate of approximately 3.5 million babies per year, half of whom are female, and then 80 to 85 percent incidence of acne in this group, my calculations indicate that between 30,000 and 75,000 female patients might require Accutane therapy per year in the United States. I have estimated comparable figures in another way. The average dermatologist in the United States probably had

between one-half and two patients per month who are of childbearing potential and who require Accutane.

In preparing for this presentation, I have asked other recognized experts in the field of acne, as well as a few practicing dermatologists to estimate the number of women of childbearing age who they think the average dermatologist might elect to treat with Accutane each month. The figures that they estimated ran up to six patients per month. Using a more conservative figure to one half to one patients per month and considering the fact that there are approximately 7,000 practicing dermatologists in the United States, my calculations reveal that between 40,000 and 84,000 women of childbearing potential might be candidates for Accutane each year.

If one compares these figures to the actual usage of the drug, the numbers are in a similar range. I mention this because it's been stated that there is massive over usage of the drug and its use must be cut drastically. I will not argue with the point that there are instances where the drug is used inappropriately. I will argue against the point that the drug has been grossly overused, based upon the calculations that I have presented. Although with the new pregnancy warning program, it's my belief that the number of patients who are going to be treated will be decreased.

Some of those who are opposed to the drug suggested

some type of limited availability of the drug, such as restriction of its use to a few major medical centers. Will this work? I personally think that this will deprive a large segment of the population of the availability of the drug.

The next two slides that I am showing are the before and after pictures of a patient who participated in our early experimental studies in the late 1970's. This is the follow-up. This patient commuted from Oklahoma, but this was at a time when the economy in Oklahoma was favorable and his family could afford to send him via commercial airlines to Iowa City. Furthermore, he was only treated for eight weeks which we now consider to be an inadequate time period in terms of protecting a patient against recurrence of nodular cystic acne.

To require a patient such as this to go to a few regional centers, scattered throughout the country, would place a severe economic burden on a great majority of the patients requiring this drug. Can I ask a patient who lives in Sioux City in the western part of Iowa to travel for approximately six hours each way every month in order for me to provide follow-up care and instructions for them for the treatment of their disease? Certainly patients living in rural areas would find it impossible to get adequate treatment with Accutane.

Furthermore, considering the fact that the figures

that I have presented represented only those patients who were of childbearing potential, and they represent probably only about 40 percent of those patients who require Accutane therapy, the numbers are staggering. The regional centers would not be able to handle all the patients, particularly if they were to observe the requirements for strict follow-up visits once a month. If 150,000 patients were to be seen in 10 centers with five monthly visits per patient, each center would have to handle 75,000 patient visits per year.

Another problem that must be considered is what type of behavior patterns will be observed if the drug is restricted or removed from the market. There is no drug to replace Accutane and patients and physicians are aware of this. I am afraid that if there is restricted distribution of the drug, we will see a behavioral pattern among patients and physicians similar to that observed at the time the drug received publicity before it was available on the market. The drug will be obtained through illicit channels and may be manufactured illicitly. Moreover, patients will take the drug without physician supervision.

Substitutes, such as very high doses of readily available Vitamin A will be used with comparable or greater potential for teratogenesis. I happen to feel it is much better to have a highly educated physician and patient population who are fully aware of the dangers of the drug. I

think that the American Academy of Dermatology and Hoffman-LaRoche are making great strides to educate all of those who are prescribing or using the drug. In fact, I know of no similar effort that is ever been mounted in relation to a marketed drug.

This extensive package of educational material has not been used for a sufficient length of time to observe whether there is a change in behavioral pattern. I am confident that a change will occur and I can tell you that dermatologists such as myself who are interested in this drug, are making considerable effort to improve our education activities related to the potential for teratogenesis.

For instance, I gave talks on the teratogenic potential of Accutane at two of the largest symposiums and annual meeting of the American Academy of Dermatology in December of 1988, and will similarly give two talks this year at the annual meeting. It is my main talk now in the lecture circuit. In conversations with dermatologists around the country, I find that they are using the educational materials, and patients who I see on referral, I find that the information relating to the hazards of the drug are being adequately explained to the patients.

Let me emphasize that there has been insufficient time to determine whether these programs will work. I am confident that they that they will. Let me close by just

showing photographs of two more patients who I've recently seen. The first is a male whose disease was so severe that he had to be hospitalized. This is a close up of some of his lesions. He is just finishing his first course of Accutane and the type of improvement that we have seen in this patient is shown in this photograph.

The second patient I just saw last Tuesday. She appeared in my office referred by an outside physician. She'd been on Accutane for about one month, started by a competent dermatologist in another part of our State. I've now been asked to follow her because of the severity of her disease. Unfortunately, I do not have any pretreatment pictures. The patient told me that she was already considerably improved when these photographs were taken last Tuesday. You can imagine how she looked before Accutane was started. She started on a contraception program one month before starting the drug. She is having pregnancy tests and she is being followed by all of the rules established for the drug.

We in our hospital have the monitoring of the female patients with Accutane as part of our quality assurance program that we look at most closely. I feel that we cannot deny either male or female patients the availability of a treatment that will prevent lifelong physical and psychological scarring. I pledge the dermatologists' coopera-

tion in making certain that the necessary surveillance is conducted and that we do see that pregnancy is reduced. I thank you for your listening.

DR. PENNEYS: Thank you, Dr. Strauss. Are there any questions for Dr. Strauss and the committee at this time?

[No response.]

DR. CUNNINGHAM: Last year when we met with you Dr. Delbecki had outlined our goals and they remain the same today, as they did in April of '88. We would very much like to limit the use of the drug to the severe recalcitrant cystic acne which you've seen described this morning.

A major part of preventing malformations, of course, is excluding pregnancy. And we wish to with our program exclude pregnancy at the time of initiation of this drug and throughout the use of the drug. Ensuring contraception is a very important physician/patient cooperation. It's a contract with the two. It's a very intimate relationship, and this is certainly at the heart of the pregnancy prevention effort.

The actions that we've taken since 1988 are outlined as the package interested revision which Dr. Evans has described. Dr. Armstrong will now describe the pregnancy prevention program, the blister packaging, the multiple communications with other organizations, and the interactions with other organizations which have been taken since April

1988. Dr. Armstrong?

DR. ARMSTRONG: Thank you, Dr. Cunningham. The actions which Roche has taken to implement these three goals can be divided into three parts. The parts are the revisions of the package insert, the pregnancy prevention kit, and the new packaging introduced last week.

I'd like to start with the revision of the package insert. The first thing that was done with the package insert was to introduce the avoid pregnancy symbol, as a simple means of conveying the message, "do not become pregnant while taking this drug." This symbol recurs throughout the program and you'll see illustrations of it appearance to reinforce this very simple and very important message.

The contraindication and warning section has also been increased. Not only has the type size increased, but there's been additional detail provided within this boxed warning. In particular, there are increased warnings of the extremely high risk of malformations occurring should this drug be taken during pregnancy, and it also stipulates that there is no amount of drug and no short period of drug exposure which does not carry a risk. It also stipulates that any exposure carries the potential for these extremely severe risks.

The next section, the lower section that's indicated there also reviews what some of these more severe side

effects and birth defects can be. A very important part of this expanded contraindication and warning section is this specification of six criteria which must be met before it is reasonable to treat women with this drug.

The first of these six criteria relate to the appropriate use of the drug and specifies that it only be used in patients who have severe recalcitrant cystic acne and who have been treated with other forms of therapy without success. The second and third points relate to the patient's ability to understand the nature of the problem and carry out instructions and in particular her ability to follow-through with the mandatory contraceptive measures. The fourth point relates to the process of informed consent. It specifies that patients receive both oral and written warnings of the possibility of birth defects occurring and also the possibility of any contraceptive technique having incidence of failure.

The last two of these indications include the use of a serum pregnancy test, no more than two weeks before the drug is started with a negative result, and finally the specification that the medication only be begun on the second or third day of the next normal menstrual cycle.

The package insert also recommends that abstinence or two forms of contraception be used. This recommendation covers a period starting one month before treatment, continu-

ing through the entire course of treatment, and for one month after the last medication is taken. And this warning section now also recommends that Accutane only be used by experienced practitioners, that is, practitioners who have special competence in the diagnosis and treatment of cystic acne, doctors who are familiar with the use of systemic retinoids, and who understand the risk of teratogenic effects taking place if the drug should be taken during pregnancy. Finally, the package insert now includes this consent form which I will discuss in a little bit greater detail later in the presentation.

So to summarize, the new package insert includes the avoid pregnancy symbol, it expands the contraindication and warning section, in particular illustrates six criteria that are necessary for this drug to be appropriate in the use for females, and it recommends that abstinence or two forms of contraception be used for the entire period of treatment, one month before and one month after. And finally incorporates the consent form.

Now the package insert revisions were approved last year in August, and it was implemented by being placed in the packaging one week later. Also one week later, the revised package insert with an explanatory letter was sent to 7,700 dermatologists, and the following week a half a million physicians and 62,000 pharmacies across the country also

received explanatory letters and copies of the revised package insert, so that all those who are most likely to have interactions with patients would have this new information available to them.

In addition to the package insert, these pregnancy prevention kits were distributed to physicians. This kit is designed to provide a comprehensive spectrum of information to support the correct use of this drug and it's organized in a step wise fashion to provide a logical means of approaching the prescribing of this drug to women of childbearing potential. So let's go through the steps.

The first step is a qualification check list. This is meant to determine that it is appropriate for a woman to be a candidate for taking this drug and it specifies each of the criteria that are appearing in the new revised package insert, and goes through them in the same order which we discussed previously. There is one additional point which is made as the last question, and that is, that the woman not be a nursing mother and that she not take Accutane until after she is completed her nursing.

In keeping with this new program, the patient information brochure has been revised and updated, and this information describes, not only those effects which can occur with the drug in general, but it emphasizes the effects that may occur if taken during pregnancy. Some patients may

prefer to receive this information in a verbal fashion, rather than in a written one, and it is possible for such patients to dial an 800 number and hear this kind of information presented, either in English or in Spanish as they feel appropriate.

There are a number of misconceptions about birth control and to avoid these problems, we've also included a book containing facts that are important in understanding birth control and how it should be properly chosen and used. Many physicians, and in particular, physicians such as myself, don't feel a special expertise in prescribing and selecting contraceptive measures, and in order to address that need, there is a contraceptive referral program. Under this program it's possible to refer a patient to a gynecologist or other expert physician for advice and for a serum pregnancy test. And if both of those things are done together, Roche will reimburse for the cost, both of the consultation with the gynecologist and also for the cost of the pregnancy testing.

The next step in this process includes the consent procedures. There's a booklet here that outlines how the different elements can contribute to the physician's consent process. One of the things that we've provided is a patient self-evaluation test. This self-evaluation test goes through the same criteria that are outlined in the package insert

regarding the appropriate indication, the appropriate attempt to use other forms of treatment, the necessary information regarding contraceptive practices, and so on.

And I'd like you to appreciate that this self-evaluation test is something that the patient can take home. There's a copy that's provided for her, so that she may take it home and be able to refer to this information at any time that she wishes to. And then the final part of this consent process is the actual consent form and there are areas provided where patients can indicate that they've been informed of each of these different points from the program. Each of these six criteria that were mentioned in the package insert are reviewed in this consent form.

There are several additional points, including the fact that birth defects are not the only important side effects of Accutane, and that the patient needs to be aware of those. It also informs the patient that there is a follow-up survey which she may participate in. A final thing to mention about the patient consent form is that it does inform her that she is eligible for participation in this contraceptive counseling program with the cost of that program being borne by Roche.

So in conclusion on the pregnancy prevention kit, there are a number of items that are provided. There's a qualification check list, there's several different ways in

which information can be given to the patient, both in written information and in verbal information available by telephone, and the possibility of referral to a consulting physician. In addition, there are items that support the obtaining of informed consent from these patients.

Now what is the impact of this kit? We've had a survey done to investigate what has happened with this kit in the months of February and March of this year. This survey indicates that 95 percent of dermatologists have received the kit and among those who have the kit, 55 percent report that they have used one or more components just in the last two months. I'd also like to point out a very important statistic here that among those physicians who had not used the kit, 36 percent said that they had not evaluated any female patients that they considered to be an appropriate candidate during the period.

When you consider those two groups, you can see that 91 percent of the practicing physicians surveyed had either used the kit or had not had a patient for whom the kit was appropriate.

Now this slide gives you an indication about how individual components of the kit have been used. You can see that the referral for contraceptive counseling has been used by about 40 percent of the physicians who were surveyed, about two-thirds of the physicians used the patient self-help

test and also the contraception pamphlet, and even higher percentage, about three-quarters of physicians used the qualification check list, the serum pregnancy test or the consent form as provided by LaRoche. And even higher percentage, 90 percent, were using the patient information brochure.

Now if you consider the number of women who are evaluated using this kit, this survey indicated that there was actually a 22 percent number of patients who were evaluated using the kit who did not receive Accutane, as a result of their being evaluated with this process. And this, I think, is an indication of the critical nature with which physicians are approaching the prescribing of Accutane to their female patients. It also goes along with information that we're getting anecdotally from physicians and also from pharmacists that they are prescribing Accutane must less frequently to women.

Now the final thing that I'd like to discuss on the aspects of the pregnancy prevention program is the new packaging. The new packaging introduces a blister package that includes 10 capsules. I'd like to draw your attention to two items. On the front page of the packaging, this may not be legible since it's in red, so I'll read it for you. The first thing is that the pharmacist is requested to dispense this packaging intact. And I'll show you just

shortly the importance of that recommendation. And the second recommendation is to the patient and requests that the patient read this information carefully and thoroughly.

Now the reason that we particularly want the package to be dispensed intact is that it provides an extensive amount of information drawn from the revised patient information. This is an integral part of the packaging. It's a hard cardboard piece which not only is attached to, but actually wraps around the capsules themselves. The new packaging reinforces the pregnancy warnings by describing them in red in multiple places throughout the packaging. It also uses the avoid pregnancy symbol repeatedly and in particular when the pills are removed from the blister packaging, they must be removed through one of these avoid pregnancy symbols, as a constant reminder of the simple importance of avoiding pregnancy while the drug is being used.

The new packaging also includes line drawings illustrating some of the malformations which might be seen, but it also provides a description of other malformations of the central nervous system, the cardiovascular system, and other internal organs which are not easily illustrated. And finally, the new packaging encloses this enrollment form for the follow-up survey which you'll be hearing about shortly from Dr. Allen Mitchell.

So the new packaging introduces a blister package containing 10 capsules. It incorporates the revised patient information as an integral part. It reinforces pregnancy warnings in red. It introduces the avoid pregnancy symbol in a way to emphasize the importance of continuing with an adequate contraceptive program. It includes line drawings to illustrate the malformations which can be associated with Accutane's use during pregnancy, and it includes an enrollment form for the follow-up survey.

Now the new packaging, the pregnancy prevention kit, and the revised package insert are not sufficient by themselves. There was a need for communication of these items to the medical community. We've chosen several different means of communication to get this message to the medical community. We've already talked about the mailing of the package insert and an explanatory letter to physicians and pharmacies that occurred in September last year.

The pregnancy prevention program, including the kit was announced to dermatologists, as well as other physicians who had been identified as Accutane prescribers, but who were not dermatologists. That process also began in September of last year. A letter was sent to obstetricians and gynecologists in December in December to inform them about their possible participation in the referral program, so that they would be aware of the program and how to participate in it.

And finally, follow-up information about the survey was distributed to dermatologists in both December of last year and January of this year. All of these things by a direct mailing campaign.

But there is also some advantage in a direct, personal presentation and so I'd like you to review with me these figures about presentations made by Roche professional representatives, not only to individual practitioners, but also to dermatology departments where they might be speaking to attending physicians, residents, nurses, and other health care employees.

I'll do the rough addition for you by pointing out that in the seven-week period during September and October in which this program was initiated, there were 10,000 such visits made across the United States. And the next four months, there was an additional 10,000 visits made. Some of these were initial presentations, some of them were review or reinforcing presentations. We certainly wanted to make sure that this information was provided to the practicing physicians.

Another form of communications is in published material. I've selected three, not the entire list of possible publications, but three as illustrations of the kind of information which we have felt is important to share with the medical community. The first and the third were editor-

ials that were published, the first in the Journal of the American Academy of Dermatology, the second in the Video Journal of Dermatology, stressing the importance of this issue of Accutane and teratogenicity. The second publication was one published in the Achieves of Dermatology and seeks to avoid the misinformation that the effects of Accutane continue for a long period of time, and addresses the issue of the safety of pregnancy after Accutane has been discontinued.

It's also been a part of this program to present information at various meetings, again I don't intend to present an exhaustive list, I've instead chosen some of the more important areas and forums in which we've had direct participation in these presentations. The American Academy of Dermatology Annual Meeting has already been discussed. There was also a presentation on the Conference on Patient Education, a group sponsored by the American Academy of Family Physicians. Presentations were also made by Roche at the Annual Winter Toxicology Forum and the FASEB Summer Conference on Retinoids, and just last week there was a basic science conference held on the issues of retinoids and teratogenesis. Additional presentations have been made at State and local dermatologic societies.

Dr. Evans early this morning referred to the request to provide this information in the form of advertise-

ments. This particular advertisement is directed at the dermatology population and as you can see from the bold print, it says that there is a problem that can occur with Accutane and that it also can be avoided, and provides information about how to avoid the problem. And as you can see, here's another instance where the avoid pregnancy symbol is being used to reinforce this simple message.

This advertisement ran in primarily dermatologic publications which are listed for you here, and I'd like to point out that these journals have indicated that this advertisement has among the highest recognition and recall of any of the advertisements that they ran during this period of time. Here's also an advertisement that was directed for non-dermatologists and which appeared in other more generally circulated medical publications. This advertisement stresses that Accutane is contraindicated. And then the physician must read the finer print to find out the exceptions to that contraindication, and this does draw on the same six points that were presented earlier from the package insert.

To show the publications where this advertisement appeared, the list is provided for you, and from that list I would like to select the Journal of the American Medical Association and also Modern Medicine. Both of these publications have indicated to Roche that these advertisements were extremely well recognized and had a high recognition and

recall factor among their readership.

Finally, Roche has interacted with a number of different organizations with a number of different groups represented. We've given you some indication of the degree of involvement that we've had in discussions with the American Academy of Dermatology. We've also had discussions with the American Academy of Pediatrics and the Society of Pediatric Dermatology. We've had interactions with the American College of Obstetrics and Gynecology, and we've also met with a half of dozen professional pharmacy associations to discuss ways in which pharmacies could contribute to this pregnancy prevention program.

We provided technical advisers who have met with the Slone Epidemiology Unit in the design of the follow-up survey which you're going to hear about very shortly, and we've had meetings with the March of Dimes Birth Defects Foundation to discuss ways in which the general population could be educated about this problem.

So to summarize, we've developed a comprehensive effort and the effort has been designed as part of an integrated program. This program involves a number of unprecedented measures, things which had not been done previously for prescription medication. We've introduced the avoid pregnancy symbol, and I understand that that's been adapted by at least one other company for a product already.

We've introduced the pregnancy prevention program. Two of the most components of that are the consent form and the contraception referral program where contraceptive advice and pregnancy testing can be done at Roche expense. And we've also introduced this new blister packaging which is designed to make sure that the medication and the warnings are presented to the patients at the same time. Within this blister packaging is another opportunity for patients to enroll in the follow-up survey.

So I'd like to now close my remarks by making three observations about the meaning of these efforts. I think they illustrate that Roche is demonstrated a commitment to practicing the best medicine possible. I think they illustrate a willingness to learn from our experience and from the suggestion of others. And finally, a willingness to implement and take action on that experience and those suggestions. Thank you very much.

DR. PENNEYS: Dr. Cunningham, we are running behind schedule, if you could try to expedite this.

DR. CUNNINGHAM: I'd like to very briefly demonstrate some of the usage that illustrates the downward trend in total patients, new patients, and most importantly in new female patients. I think you can see from this graphic display that the usage of the drug peaked in 1983. At the same time we first heard about birth defects associated with

the drug and there was a decrease, a slight peak in '85, and then a steady downward trend thereafter. This doesn't show terribly well in this graphic scale, but between 1987 and 1988, there was a more significant downward trend in the usage of the drug in new female patients.

This is from the PDS data base and I won't go into the details of the other data bases, but to some extent, especially in 1987 to 1988, the other data bases demonstrate again a downward trend. I would emphasize that these are not absolute numbers, but they are trends and that is the most important usage of the data bases that we've looked at. Additionally people have asked about factory units, and without becoming too complicated, I would say that compared to 1987, our 1988 third and fourth quarter factory units showed a decrease from 1987 usage.

It is very difficult to convert those factory units into actual patient numbers because of difference in dosage and duration of therapy, but we do see a downward trend. Furthermore, in early 1989, we also see a downward trend in the usage of the drug in terms of factory units.

I'd like to introduce Dr. LaBraico who will discuss briefly with you the epidemiology of pregnancy exposures.

DR. LaBRAICO: Good morning. As background information, I would like to present the pregnancy data that was shown at the meeting last year. At that time, as of

January 31, 1988, there were a total 363 reports that had come to Roche via the spontaneous reporting system. And I would indicate to you that we're talking now about the year that therapy was initiated. At a later point, I will show you some information regarding the birth. Year of birth-- 363 with a total of 61 congenital malformations. The peak year for reporting was 1983 and 1984.

This information is now as of April 30, 1988 and it's a little bit of a variance with the information you received by mail, because we've updated one additional month. The information you received was as of the end of March. This is as the end of April. There's a total of 426 reports since January 31, 1981, an additional 63 reports. There have been 14 additional reports of congenital malformations, two occurring in 1988, one in 1984, and the rest occurring in 1986 and 1987. Again, when one looks at the total trend in reports, the peak years occurred in 1983 and 1984 with a downward trend since that time.

Of these reports, about half have occurred in the years 1988 and 1989; 14 reports have occurred since October 1, 1988. And I used that date because, as you heard from Dr. Armstrong, the pregnancy prevention program was initiated at that time, and has continued its implementation through the first quarter of this year, and I'll get back to that in a moment.

This is a slide showing the information as of April 30th on congenital malformations by year of birth. The peak years again, 1983 and 1984, with two births in 1988. Again, showing that the peak events occurred in these two years and with a downward trend since that time.

As I have indicated, we have received 14 additional reports since the 1st of October when the pregnancy program was initiated. I would like to take a moment to reflect on what we've seen from that recognize and realize that we're talking about the program that has just been initiated and that the numbers are small, but I think it is of some use to look at the information that we can gleam from these reports.

What has happened from the standpoint of pregnancy prevention in these early cases? There are a few cases where failure to comply with the following guidelines, either performing a pregnancy test or waiting to the second or third day of the next menstrual period before starting therapy. What has happened in these situations, in one case a woman presented with a history of infertility and a pregnancy test was not done. Another situation, the pregnancy test was done, but probably one or two days after conception, but therapy was started before waiting until the next menstrual cycle.

The larger number of cases occur in the area that I'm referring to is contraceptive failure. Most of these are

in the err of human failure. The women are counseled, they understood the risk, but for some reason failed to use their method of contraception at the appropriate time. We feel that the blister pack that Dr. Armstrong described would provide a constant reminder to this group of the need to maintain contraception at all periods of time. Just the fact that every time they have to take their medication, they will be reminded by the pregnancy symbol that appears, as Dr. Armstrong has described.

Method failure is a little bit more difficult to assess. It does appear that in two of the cases, there may have been a true method failure. But certainly I think that the need of recall appears to be a very important factor in reminding women that they must continue the contraception. There were a few cases of self-medication. These were patients who had actually been treated in the past with Accutane and used some leftover medication from a prior prescription. And again, I think that the blister pack would have provided information and a reminder in these situations to a woman that she must maintain contraception.

We will continue to monitor these new reports as they come in looking for risk factors associated with these pregnancy prevention failures. At this time, I will introduce Dr. Mitchell, who will discuss the follow-up survey.

DR. MITCHELL: Thank you. I'll try to keep my

remarks as brief as I can. We have been asked by Roche to design and carry out a follow-up survey of women who have been treated with Accutane. The objectives of this survey are to determine the rate of pregnancy among women who use Accutane, their awareness of the teratogenic risks, their history of prior acne therapy, pregnancy outcome among women who do become pregnant, risk factors for the occurrence of pregnancy, and to assess the impact of an intensive survey on the compliance with prescribing guidelines.

It's important to bear in mind the period of interest of this survey. As was mentioned, the typical course of Accutane treatment is approximately five months, and what we have determined is a reasonable period in which to monitor any pregnancies that might occur during the period of Accutane treatment, including the very last few weeks is a period of approximately six months, two trimesters of time following the last treatment with Accutane.

The Slone Epidemiology Unit at the Boston University, School of Public Health is responsible for the design and the development of the protocol for data collection, data processing, data analysis, and this is all being done under very helpful guidance provided by an independent SEU Accutane advisory committee appointed solely by the SEU. You may not be able to read this, but the panel is chaired by Dr. Paul Stolley and includes both academically based and private

practice based dermatologists, people with pharmaceutical expertise, pediatric expertise, teratology expertise, and as was mentioned earlier, we have Dr. LaBraico and Dr. Dai from Roche who provide liaison.

It's important to recognize in designing the survey that there is a specific context in which it is being conducted. First, the survey monitors physician and patient compliance with the Roche pregnancy prevention program. Because physician and patient compliance with the pregnancy prevention program is voluntary, survey participation is necessarily voluntary as well. This raises the concern because survey participation is voluntary, the population surveyed may not be representative of all women who use Accutane. The likelihood that the surveyed sample will be representative increases as participation increase, and therefore the survey designed should seek to maximize enrollment.

Let me briefly review the major components of the survey that we have designed. First, as I mentioned, it involves voluntary enrollment. Enrollment will be through the physician or the medication package. Each patient will be followed for six months after the discontinuation of Accutane or for a period of approximately 11 months. Follow-up will be conducted either by telephone or by mail, and there will be an effort to assess both the completeness and

the representativeness of the survey.

I'd like to consider some of these points in detail. First the enrollment. When confronted by this prescribing sequence, we have a variety of options through which we might be able to enroll women in the survey. Remember the woman goes to her physician who prescribes Accutane, she takes that prescription to the pharmacist who fills the medication, and the woman then consumes the medication. Well, at any step along this way, one could theoretically offer an enrollment opportunity, and we have elected to utilize two points in the enrollment procedure.

These are the physician generated approach in which the physician asks the patient to complete the enrollment form at the time of Accutane prescription, and the medication package generated approach in which the medication package contains an enrollment form which the patient can complete. Now we also considered the issue of payment as an incentive for an enrollment. Survey participation can be enhanced, we believe, by offering payment to patients for their enrollment. However, payment to physicians would be inappropriate, as it might serve to encourage Accutane prescribing.

Let us know consider the characteristics of each of the enrollment approaches I mentioned. First, the physician generated approach. All Accutane prescriptions originate with the physician. It is a logistically feasible approach

because it can easily be added to the pregnancy prevention program. And finally, the physician's encouragement provides a strong incentive to the patient to enroll. The enrollment forms as has been mentioned are included with the pregnancy prevention program materials, and they're actually attached to the informed consent, and it requests a relatively limited amount of information to be completed.

The medication package generated enrollment approach provides different opportunities. It first of all, provides a second enrollment opportunity directly to the patient, bypassing the prescribing physician. It provides a payment for enrollment which is a familiar process must akin to the consumer rebates and a form that's easy to complete. It may identify through differential enrollment non-complying physicians and it may preferentially target women who were either not enrolled by their physicians or who are non-compliant but attracted by payment. That form, as has been shown, is a smaller version of the other enrollment form, the physician generated enrollment form, and is included in the medication package.

Let me present a schematic overview of the survey design. As we mentioned women may enroll in the survey, either prompted by the medication package or the physician. Upon enrollment, they are sent a check, a payment of $10.00 for their enrollment and then they are followed for a period

of approximately five months during their Accutane therapy and for that six-month period following termination of Accutane therapy.

Women are enrolled either into the telephone follow-up arm of the survey or the mail follow-up arm. These two have different characteristics. The telephone follow-up arm involves a telephone contact shortly after enrollment at approximately two weeks. Another telephone contact during approximately the middle portion of Accutane treatment, and a final telephone follow-up at six months following discontinuation of the drug, or 11 months following initiation of the drug.

Mail contact or mail follow-up on the other hand differs primarily in that there is no contact, other than the payment. There is no contact during the period of therapy. There is a mail contact at approximately six, basically to maintain the cohort so that we can continue following. And the follow-up that does occur, the major follow-up is at 11 months and obtains similar information to that obtained in the telephone follow-up at 11 months following the initiation of therapy.

The information that's sought from the two components is both similar and different. Pregnancy occurrences and if there are pregnancies, their outcomes are identified both through the mail follow-up and the telephone follow-up,

since that information is obtained after the completion of Accutane therapy. On the other hand, such as acne history and most importantly risk factors for the occurrence of pregnancy, we believe is only valuable if collected prospectively, and therefore that information is uniquely obtained through the telephone survey. All information that is obtained is confidential. No identifying information will be provided to Roche, FDA or others without specific written consent from the patient.

Let me try now to review what's happened in the weeks since the survey has been initiated. As has been mentioned, the initiation of the survey was announced at the American Academy of Dermatology Annual Meeting in December, and at that time and the weeks following there was initial distribution of the survey enrollment forms. In January of '89 this year, the physician generated enrollment approach began in earnest. And in the first four months of this year, there have been a number of activities, some of which have been mentioned.

Enhancement of the physician generated enrollment approach, both to dermatologists and non-dermatologists and through an endorsement by the Academy of Dermatology direct mail, advertisements, visits by sales representatives, we have had refinement of the follow-up procedures, we have developed a pregnancy follow-up protocol with Dr. Edward Lammer, and we

have initiated the survey assessment activities primarily in a prescription based system in Rhode Island, and in discussions with various closed panel health plans which are now underway.

This histogram describes the absolute number of enrollments in the various weeks of the survey. I believe there's a total of 14 weeks. Members of the committee who have seen the quarterly report will notice that that ended here. We've added the most recent information we could which is the last two weeks in April, and as you can see enrollments have totaled, 1,306 in this period, and at the present time or as of a week or two ago, they had increased to approximately 105 per week. We're more interested in the slope of this curve rather than the absolute numbers. This represents the early weeks of the enrollment process.

Remember all of these enrollments have come solely through the physician generated approach since the medication package was not available with the enrollment form. We've also completed at this point approximately 625 telephone interviews. As one would expect, one should encounter some pregnancies and we have, and as a matter of fact at the very end of last week, we encountered the first two pregnancies, and we obviously don't have any more current information than that.

In such unique undertaking we would expect to

encounter some problems and we have. There have been three areas of problems. First related to the instant start up of the survey with no pilot experience and no introductory phase. Two, the physician generated enrollment approach, because of start up difficulties, there was initial confusion as to the actual existence to the survey. There was confusion as to the availability of enrollment forms, and there was incomplete awareness of the survey. As has been mentioned, the medication package generated approach was hampered by the absence of the vehicle and that package has now been introduced.

What has happened to resolve these problems? In terms of the instant start up, we have incorporated our early experience into the ongoing activities of the survey. We have compressed and enhanced the introductory efforts. In the physician generated enrollment approach, physician education has been enhanced; the distribution of enrollment forms has been enhanced. We are in the process of developing a newsletter at the suggestion of our advisory committee to provide feedback to participating physicians.

And in terms of the medication package generated enrollment approach, obviously with the introduction of the new package, we hope to see an increase in enrollment, a substantial increase. We are exploring with Roche a pharmacy involvement to encourage and enhance enrollment, and we will

be establishing a toll free telephone number, so that women who choose to, can directly enroll in the survey.

We anticipate a number of areas of activity in terms of enrollment enhancement. The physician generated aspect will again be the subject of direct mail, the sales representative visits, advertisements, meetings, and newsletter I mentioned. The medication package will involve, not only the introduction of the package, but the availability of the toll free telephone. We will concentrate obviously on the follow-up of the enrolled sample, both the telephone and mail arms of that follow-up, and we will devote considerable attention to the assessment of the completeness and the representativeness of the enrolled sample.

And let me just touch on those two components. In terms of the completeness of this survey sample, we intend to assess enrollments in relation to overall sales, according to the source of enrollment, the differential sources, the physician versus medication package, and according to defined sub-populations. One that we're working actively with is located in Rhode Island, a State based prescription registry, and others that we're currently in the midst of negotiations, closed panel, health plans, such as Medicaid, HMOs and private insurance schemes.

In terms of the representativeness of the surveyed sample within those defined sub-populations, we hope to

compare the characteristics of the enrolled and unenrolled women who use Accutane, and secondly, to compare pregnancy rates among enrolled and unenrolled women who use Accutane.

I'm sure the committee is concerned about the availability of survey findings; we certainly are. Given that each enrolled woman will be followed for 11 months, complete results for any cohort of participants will become available approximately one year after enrollment. Thus, complete follow-up information on the women enrolled to date, January through April, will become available in the spring of 1990.

However, interim findings will be provided both to Roche and to FDA at two levels. First, immediate communication of the occurrence of pregnancies and the effect of those occurrences on the pregnancy rates as we can define them. And second, in our regular quarterly report in which we describe absolute enrollments, as well as enrollment rates as best they can be estimated, and the results of the telephone and mail follow-up components of this survey, with particular focus on physician and patient compliance.

We're pleased to be able to describe the early stages of this survey to the committee and be happy to respond to any questions you have at the appropriate time. Thank you.

DR. CUNNINGHAM: I'll take just about five minutes

and then we will be complete. I realize we're behind schedule. I think this morning you've heard the history of Accutane; you've heard what took place last April, you've heard what has taken place since that time, and I'd like to just outline for you what we anticipate the next steps will be.

The blister packaging has been fully described. It's clear that with its introduction last week, it has not had a chance to make a full impact yet, and we believe that it will be a very significant impact. The Slone follow-up study just described, clearly again, is in the follow-up phase and its major impact and its results will come in the next few months.

We haven't described in very much detail, but it will be available next month, a CME videotape which is the first step in our program of continuing medical education for health professionals. It includes a videotape and a monograph. There is one available for you to look at later. It's at the committee's table and we can show it on the video monitor, if you choose. It's entitled, "When Medicine and Conception Collide." We believe it is truly the highest standard of practice endorsement, and we intend to continue on this road.

Direct mail, of course, has been a primary vehicle for us. Every time we've had anything of significance, we've

communicated directly to all dermatologists immediately. Many of the times, we've communicated to the more than half a million physicians in the country and also all pharmacies. That will be a continuing effort on our part to keep everyone up-to-date in this situation.

The advertising you've seen is rather dramatically focused on contraindication and proper usage of pregnancy prevention. It is not focused on usage. The two ads you've seen are representative of the type of advertising you will see in the future.

The pharmacy interaction has been described. It is in its implementation stages. All of the major pharmacy associations have been contacted. They are very interested and some degree of participation with our cooperative efforts in terms of pregnancy reduction and prevention. Our professional representatives will be calling on all dermatologists again in the next few months. Between May and December of 1989, we expect that there will be another 20,000 visits with complete information, the pregnancy prevention program reemphasis and all matters pertinent to the pregnancy prevention issue.

Finally, I think we'd like to summarize by saying that we intend to monitor this situation and revise as needed. I think I'd like to summarize that this has been an update this morning. The medical need for this drug, I think

has been described. I think you see it's unique. It's unquestioned. It's a truly a revolutionary medication in many ways. And on the other side of the coin is certainly the most significant and most emotional impact one could have that of human malformations. We believe that the threat of human malformation, and if Accutane is used during pregnancy is serious. I think everyone in this room considers it so, and has treated it thus.

Concerted efforts, we believe have resulted in some progress. I think you've seen some graphs. There has been some trend in malformations which is definitely downward. The downward trend in pregnancy is also encouraging, and the downward trend in usage, we feel is also a sign that the physician and the patient is truly aware that the goals of using this in severe recalcitrant cystic acne and excluding pregnancy and ensuring contraception are meaningful to them.

On the other hand, we don't feel we're at our goal yet. This is clearly a very serious issue. Last year, I heard one of the speakers refer to the wisdom of Solomon that was necessary to come to a solution to this problem, and I believe that probably is necessary. I think you've heard many speakers describe the program. It's been implemented rather recently. It will need some time to make its full impact. Some impact has been felt. We have seen some downward trends since its implementation. We've had very

many anecdotal experiences, as well from physicians and patients saying that they are treating this medication a little differently than they did in 1982. And we see that as positive.

Our pregnancy prevention program was meant to be a comprehensive effort and I think you've seen this morning that it is. It was meant to be integrated. It goes as Robert Armstrong said from the issue of the package insert to our pregnancy prevention kit to the issue of the packaging and the reminder to the patient with each capsule, I think, is going to be a significant impact in the future.

Finally, I'd like to say that we have appreciated the input of the group and the committee, and the Food and Drug Administration since 1983, when we've been working in concert to solve this difficult problem. Thank you.

DR. PENNEYS: Are there any questions from the committee for the presenters from Hoffman-LaRoche? Dr. Fleiss?

DR. FLEISS: May I ask one of Dr. Mitchell? Of the women already enrolled, what fraction were enrolled by dermatologists and what fraction were enrolled by other physicians?

DR. PENNEYS: Could you please repeat the question, Dr. Fleiss into the microphone?

DR. FLEISS: Of the women already enrolled in the

follow-up survey, what fraction were enrolled by dermatologists; what fraction were enrolled by other physicians?

DR. MITCHELL: I don't have that information at the moment. But they are enrolled by dermatologists, but I don't know the exact proportion.

DR. CUNNINGHAM: I can tell you though that the usage of the drug in terms of patients' treatments is approximately 70 percent dermatology and approximately 30 non-dermatology, and that has remained rather constant over the years. We have, as you've seen, primarily target of the dermatologists is our audience. We've been very careful not to promote the drug to non-dermatologists, but we do feel an obligation, especially in light of the seriousness of this problem, to fully inform those identified prescribers of Accutane, and that amounts to about 30 percent of the prescriptions. We'd be pleased to take other questions at this time or later if the chair desires.

DR. PENNEYS: Are there other questions from the committee at this time? If not, why don't we take a five-minute break.

[Recess.]

DR. PENNEYS: The next presentation is from the Office of Epidemiology and Biostatistics.

DR. STADEL: Since I've not spoken before this committee, I'd like to introduce myself. I'm Bruce Stadel.

I'm Chief of the Epidemiology Branch for the FDA. My background is, I am here after 13 years of work on research on contraceptive evaluation. So some of the experiences are related to the issues here. My professional background is that I'm board certified in preventive medicine and an epidemiologist.

I'm going to be speaking and really an interpretation of some of the things we've heard earlier, rather than in any particular contradiction to facts, but rather some perspective on what we mean. I'd like to acknowledge at the outset, the work that Dr. David Graham has done ongoing over the last year. You will recall his presentation to you a year ago, and he has been a main source of effort in the branch in developing the presentation that I'll be giving today. Also, Dr. Franz Rosa who has worked on this issue for many years.

I'm going to begin by commenting on the slow epidemiology unit because the essential problem here is the low rate of enrollment of potential participants. We have been reviewing the protocol for this study since June of 1988. I have reviewed it, my staff has reviewed it, and I have referred it for outside expert review in epidemiology and biostatistics. The opinion is uniform that one cannot validly ascertain pregnancy exposure under a voluntary enrollment mechanism of this type with any reliability.

The enrollment rate presently estimated, if use in the coming year were the same as in the last year, would be 6 percent. Now these are the women, both the women and the physicians are the volunteers. We have grave concern based upon much formal research that these are the people who will perform the best, the ones who will be the problems are the ones who won't enroll. So on that basis, I must say that I am not prepared to rely on the results of that kind of enrollment rate in advising about the rates of pregnancy exposure, about the nature of the exposed participants.

I'll now move on to the first transparency, Dr. Herrara of the branch is going to assist me. I'd like to begin here briefly showing some transparencies before the slides. The first one I refer to Dr. Cunningham's comment about a downward trend in birth defects being encouraging. I think this is a matter of great concern. But this is in fact, the best we have now. There are some slight differences you will see in numbers of defects from one slide to another because they been prepared at slightly different times. The variations are very small and they do not impact meaningfully on the overall direction of my comments.

These are the defects reported to Roche, and to our knowledge, their reports to us, and the totals reported to the FDA. As you can see, the only difference is that we received three additional defects reported total for 1988,

and I'm not sure exactly why, but again it doesn't matter very much.

If I may look at the next transparency, please. This is extremely important to understand about reporting of birth defects. The first is that we know that everything is under-reported in the spontaneous reporting system. Of vascular deaths related to oral contraceptives during the high publicity years in Britain, 15 percent were documented as reported, only 15 percent. 10 to 20 percent of deaths from sudden infant deaths syndrome in relation to diphtheria, pertussis, tetanus vaccine have been reported, and from various projects we have for serious adverse effects in general or alleged adverse effects, 1 to 5 percent in a series pilot products.

All right, so you have great under reporting, a phenomena which can be enhanced when there is increased anxiety about possible implications of reporting, that is, as pressure goes on, one can well imagine people becoming increasingly concerned about these events when they do happen. We know there is a reporting lag on an average of about five months of which for birth defects must be added to the gestational length which would tell you how likely we are now to have heard any reports in the last, say 14 months.

And we know that induced abortion rates as they can be expected to increase in pregnancy exposures will of

necessity decrease the rate of defect reporting. So these circumstances would make it most unwise to rely on trends in birth defect reporting in an effort to understand what is going on. The real issues is pregnancy exposure to the drug.

If I may have the next transparency, please. Now here we have the Accutane pregnancy exposures by number reported to Roche, as you see there were quite a large number in 1983 and 1984, but looking from 1985 to 1988, we do not see, despite considerable concern, publicity, bulletins, revisions of labeling, the pattern is not of an appreciable change in the rate of spontaneous reporting of the pregnancy exposures.

The next transparency is based upon calculations that we have done which I will explain in greater detail later. Basically, we've estimated the number of women in reproductive age who have received the drug for an average of five months each, and we applied to this the prevalence and failure rates of contraception as determined by national survey data published in 1987, cited by Dr. Michele in his Medical Progress article, March 23rd of this year.

Infractor in estimated rates of abortion based upon our own experience in analyzing the data from the Medicaid system to estimate what might be the actual range of the number of birth defects which may have occurred. We recognize that these are based on estimates. Nonetheless,

they are estimates based upon actual survey data for contraception during the period of time in which we did not see an enormous initiative towards a changing of contraceptive patterns.

The next transparency--it begins expressions that I will make in more detail later about what we believe is in evidence that Accutane is used rather more in women of reproductive age than seems reasonable. Here we have a male to female ratio estimated at a little over 5.5 to 1 for cystic acne and yet from both the PDS and the NDTI data bases, we find the ratio in males to females to be close to 1 to 1. This is one of many pieces of information which have led us to have great concern about the extent to which this drug is being used by women of reproductive age.

The next transparency and the last of the transparency group here is another way of looking at this, and that is, that we have taken a data on the female populations of various countries, reproductive age women 15 to 44 and looked at the ratio of youths in the United States versus in those countries. So the United States compared to the United States is 1 to 1, that's the base line. So our use is eight-fold higher than Sweden. Six-fold higher than United Kingdom and eight-fold higher than Germany.

These are all countries of reasonably comparable developmental standards in levels of medical care, and yet in

some way they are able to deal with the issue of Accutane use at a level of use in women of reproductive age which does seem more commensurate with the epidemiology of the disease as we know it.

Now I will now turn to the prepared slides. This is just a reminder of what a pregnancy category extra is in the Food and Drug Administration. It's one in which studies in animals or humans have demonstrated teratogenic results and which it is considered that the risk of the drug used during pregnancy outweighs any benefit of its use during pregnancy. I think this is very important in regard to my repeated emphasis that the issue is pregnancy exposure, rates of pregnancy exposure, not birth defects.

Again a reminder, as I said before about the incidence of male versus female cystic acne. One estimate, using the data from the N Haines, National Health and Nutrition Examination Survey is an incidence of about 5,000 new cases per year applying the definition.that was used in relation to the IND. As I say this is not the only figure we rely for concern. This was discussed last year, and I pointed earlier to the substantial disparity in use in the United States compared to other highly developed countries, the UK and in Europe.

Now this begins some important issues of--our figures for new starts in 1988 are virtually identical to

those of Roche. The agreement is not about the data. We came in a little under 70,000 new starts, I've forgotten exactly what they did, but the order of magnitude is similar. This shows simply--reminds you that despite the publicity, Dr. Evans discussed all the way from 1983 up, at least until 1988, there's been virtually no change in total use of Accutane by women of reproductive age or in the rate of new starts. One could say essentially, apparently no impact. We believe as I say that this is substantially in excess of what can be identified in terms of the male to female ratio.

I will show you this. This is the percent of total Accutane use in women 15 to 44, using another data set. As I say, here the ratio is nearly 1 to 1, men to women, yet the disease is vastly a disease of men.

I'll now move on to the brief summary. Although this drug is 80 to 90 percent prescribed by skin specialists, if you use our incidence figure of 5,000, then the prescribing exceeds indication by 15 to 20-fold. If you use simply the comparison to the experience in the UK and in Germany and so on, you're talking more six to eight-fold difference in the usage patterns. I don't think that one needs to argue about whether these are correct or some figure in the middle is exactly correct. The point is many orders of magnitude, inapparent disparity.

This emphasizes why a year ago, there were FDA

interventions in reducing the use of Accutane to a level commensurate with the label. And with the elimination of pregnancy exposure as was emphasized in the letter from Dr. Gavrilovich to the company in November of '88 follow-up after the main meeting, and that the question then is how well do we see thus far that these requirements appear to be being that or likely to be met? What is the projection from what we know?

This is the Accutane used by quarter from NDTI. I'd like to point out that although this is 1986, 1987, and 1988 by each quarter, there is some varying pattern, wave like pattern. There is a decrease here in total use, not accompanied by a decrease in new starts. This is of particular concern for a number of reasons. One, we know that a number of women are already pregnant when they start the drug. I've seen reports of that, I'll mention in a moment. We know that the likely pregnancy exposure among those who are not pregnant when they start, is in the first one or two prescriptions, in a large majority of cases. This is not surprising because this is the likely place of early contraceptive failure.

For example, the first year of failure rate of all contraceptives cited by Dr. Michele is 3 percent, whereas the natural for women who have been on the pill for many years is a tenth of that, and in my experience previously, although we

don't have firm figures, is that the failure rate is concentrated in the first three months of use. Which is not surprising either in terms of use failure, that is, the characteristics of women using the pill, getting used to a method or in the likelihood of some actual method failure. That is, having to do with the pill itself.

So I think that we're dealing here with--the issue is not totally abuse, but early number of new starts. The issue is exposure, pregnancy exposure occurring in the early part of Accutane use and in this area, I do not see evidence of an appreciable reduction in exposure through the fourth quarter of 1988.

Another way of looking at this is we took data from Dr. Michele's paper that looks at each pregnancy risk category, that is women not at risk because they are not sexually active and have had a hysterectomy or other such reasons. Then there are the different sterilizations, female sterilization, tubal ligation, male sterilization, oral contraceptives, condoms, IUDs. Other comprises the sponge, spermicide, and so forth, which were for a small group, and the next figure is the prevalence of use in the population, according to the 1987 report cited by Dr. Michele, originally published in Family Planning Prospectives.

The next is the first year failure rate known to pertain for that contraceptive method, again cited by Dr.

Michele. Applying this to an estimated 70,000 users with each one having an average length of Accutane use of five months, one can derive out the expected pregnancy exposures in each group. So if, in fact, the Accutane users in 1988 had used contraception in a manner similar to that established for women in the country as a whole, we would have expected just under 1,200 pregnancy exposures.

Now even at the extreme, if all of them had been on oral contraceptives, which they clearly were not, there would have been still nearly 400 with its 3 percent first year failure fate, 400 pregnancy exposures. This is because that 3 percent first failure rate is being driven by an exposure of about 70,000 women. So that even women with the best efficacy, you still wind up with a substantial number of exposures. And I emphasize it is clearly not the case, that all these women were on oral contraceptives.

In this regard, I note the nine exposures during pregnancy that were reported by Roche in the first quarter of 1989, three were already pregnant at the time of exposure, two of whom were using the diaphragm. Three were relying on condom, vasectomy or apparent female infertility, respectively. One was on oral contraceptives, and for two the contraceptive method was uncertain.

Thus, I'd also emphasize that of the eight exposures for whom the date of first Accutane use was known, six of them

were in November of 1988 or later. So this is the pregnancy exposure experience reported in the first quarter and still demonstrating on those reported an impact in terms of three of them already been pregnant, and the others relying on patterns of contraception not acceptable to the circumstances.

Again, if we had about 1,200 exposures in 1988, our experience with Medicaid data, we would expect that about 40 percent of those would undergo drug induced spontaneous abortion. I think this is probably a reasonable figure. And of the remainder, the induced abortion rate, we would expect to be on the order of twice as high as in the general population or giving about 400 in 30 induced abortions, leaving about a little under 300 coming to delivery, of whom you would expect a little over 70 to have some defect. So this is the expectation for 1988, based upon our calculations.

This is another tally of what's been reported to us. The yearly figure showed 78 because it was prepared slightly later than this slide. But this is a recent report where 74 of the 94 in hand had the classical -- retina embryopathy, and other defects included things that fell short of the classical syndrome but were reported.

In that context, I would like the last transparency. This is a 1639 Form, an adverse drug reaction report which you see the reaction onset, May of 1988, one year ago. There's a baby who was born with hydrocephalus, no left ear,

grossly deformed right ear. The indication recorded was mild acne. And this says that the dermatologist was unaware of the pregnancy and that the obstetrician was unaware of the Accutane exposure. That's one report, but I've pulled it out because it really impacted on me that, as of May 1988, you could have this constellation of events occurring.

I think it emphasizes an anecdotal form. What I have tried to express to you is the deep level of concern that we feel in the epidemiology organization about the ongoing, very high rate of use, about the apparent disparity in the use, given the male to female ratio of the disease, about the apparent continuance of pregnancy exposures, about the unreliability of using birth defects to monitor pregnancy exposure, given changes in abortion rates, and given the reality that with increasing pressures on the issue, that one might expect that reporting of pregnancy exposure itself may be something people are reluctant to do. And that we feel that under these circumstances, simply the most reliable data we have is the drug use data I've shown you, which clearly indicates excess use in relation to the indication. Thank you.

DR. PENNEYS: Do we have comments or questions from the committee? Dr. Drake?

DR. DRAKE: I'd like to ask you a question. You kept referring to the increased use of new starts of this

drug. I want to ask if any where in your analysis you consider the effect of the increased publicity around this drug had on patients who heretofore did not realize that there was a drug available to them that would help them, and in fact, many dermatologists have expressed to me that they have had many patients come to their office who had bad scarring acne, saying I did not know there was something available. But because of all the publicity surrounding the last hearing, many patients did, in fact, come in asking about their very severe acne. And I've not heard you mention whether you've stratified for that particular variable?

DR. STADEL: At first we did not refer to an increase in new starts. We said it was constant. Second, the point is that the--

DR. DRAKE: Let me correct it. I don't care if you said increased or constant, the fact remains that you were saying there was not a decrease. Is it a possible fact that there is no decrease because there are more patients demanding the drug?

DR. STADEL: I think there are any number of explanations. I think the point is that a program was initiated a year ago, a great deal of concern was expressed. There was agreement that use by women of reproductive age was in excess of indication. I'm simply pointing out that it hasn't gone down.

DR. DRAKE: You still haven't answered my question. Have you addressed the fact that there may be a greater demand for the drug, due to increased knowledge from the patients, knowing that this drug is now available to help them, which they didn't have any knowledge of prior to all of this publicity?

DR. STADEL: I'm quite willing to accept that possibility. It's not the issue addressed by the analysis. The analysis simply addressed at reporting the absence of a decline in the face of the general expression last year that the drug is used in excessive indication. The possibility of that is quite acceptable to me. Data on how a woman decided to use Accutane is not part of the NDTI or any other drug use data base. They report based upon sampling of pharmacies and sampling of physicians on the number of prescriptions and the number of mentions.

DR. DRAKE: Second question. You said that voluntary participation does not yield reliable information. Is that a correct assumption?

DR. STADEL: It can't be assumed to know, not when the volunteer participant/patient rate is extremely low, no.

DR. DRAKE: Then, let me ask you a question. Are you suggesting then that women who are of childbearing potential be forced to participate in a survey before they can get this drug?

DR. STADEL: I am advising on my assessment of an epidemiologist of what is realistic and not realistic under the circumstances. I do not consider it my world to recommend along that line. That is in the purview of other decision making capacities.

DR. PENNEYS: Dr. Schroeter?

DR. SCHROETER: You compared the usage of Accutane in Europe to that in the United States. Maybe I missed the reference of the data, would you document that data source?

DR. STADEL: David, do you have the citation?

VOICE: It was the information that we got from the CDC, and also that was published in Lansit last year on foreign use of Accutane in European countries.

DR. SCHROETER: What is the source of CDC?

VOICE: I believe it was probably INS America, the same people who provide the drug use information that we rely on for NDTI and for national prescription audit here.

DR. SCHROETER: I'd like that documentation. Thank you.

DR. STADEL: Yes, if you could give me a note afterwards as to where it says--

DR. DRAKE: I think it should be forwarded to all members of the committee. We would all like to see that documentation.

DR. STADEL: Fine.

DR. PENNEYS: Dr. Woodley?

DR. WOODLEY: Dr. Stadel, you just heard a testimony from Dr. Strauss who's an acknowledged national, international expert in acne and who basically stated that he feels that the indication for acne perhaps is about right. That 3 percent of women with acne actually have binodular cystic form that recalcitrant. I'm wondering how you reconcile the data you kept bringing up from the NDTI with that testimony?

DR. STADEL: The NDTI data on the number of women new starts, you see we've agreed between our estimates and the firm, it was about 70,000 new starts last year in women of reproductive age. Now I heard the firm state they considered that to be--that the levels had been in excess of what was appropriate. If I misheard something, perhaps you would like to correct that now. Then you do agree with that statement.

With regard to the prevalence in incidence in cystic acne itself, all I can is that there are, to my knowledge, and I've looked, there's very little by the way of systemic, properly sampled epidemiologic data using pre-agreed upon diagnostic criteria to estimate the prevalence in the incidence of cystic acne of various levels. We did use one resource which as its strength the National Health and Nutrition Examination Survey is a formally structured population based sample. There are a number of assumptions

involved, give rise to the figure of 5,000, as an annual incidence, and I acknowledge those. It's an order of magnitude, a measurement one has to use. Nonetheless, while I have great respect for practice abilities, the estimation of prevalence in incidence is an epidemiological and statistical issue.

DR. PENNEYS: Dr. Abel?

DR. ABEL: There were two difference figures mentioned today on the prescribers, the types of physicians who prescribe Accutane. One being 70 percent were dermatologists, and the other time it was mentioned that 90 percent were dermatologists. Could you clarify your statistics?

DR. STADEL: I'm quite willing to accept being--we had a figure of 80 to 90. If someone uses a different sample and comes up with a figure of 70, I'm really very unlikely to argue about it. There's a certain amount of variation that comes about in estimating these kinds of things, and it's really a question, of again, of order of magnitude. My only reason for showing that or raising it, is a concern that although the drug is being prescribed to the vast majority by those who are experts in its use and in its indications, we do continue to have these levels of concern.

DR. PENNEYS: Dr. Schroeter?

DR. SCHROETER: I'd like to address the ratio presenter. In light of the data that has been presented by

the epidemiologic unit of FDA, I would like to ask you how you expect your recent implementation of a program to reduce, number one, the teratogenic effects of the drug? Are you going to see a reduce in the amount of use? It appears that if voluntary surveillance is only going to be at the 6 percent level and indeed that those that are going to volunteer to be surveyed are to be the least likely to actually have need of that survey, in other words, probably the ones that are going to be most likely exposed and have teratogenic effects are not the ones that are going to volunteer in the survey?

DR. CUNNINGHAM: I'd like to first clarify the previous point about the usage data. I think that our presentation includes, again I don't disagree with Dr. Stadel in this general range of usage in new females for 1988 of the 65 to 70,000 new females for 1988, I think that the concern has been raised repeatedly that the usage at that level is too high for many of you on the committee and many of you in the audience. What I've tried to say today is that the usage trends we believe are down to some extent and that we see some usage trends in 1989 in our own factory units that tend to go downward as well.

I think that to our mind it is not the central issue. The central issue in our mind is malformations and secondarily, pregnancies, and usage is the secondary issue.

I agree with the possible extrapolations from numbers of usage to numbers of pregnancies, but I think under these very special circumstances we probably have the most informed population on the face of the earth in a way with the dermatologic community and the patient, hopefully are going to be in very close harmony on this issue of contraception.

I don't want to either get into a debate though about the numbers, because I think we've all agreed that's not the central issue. Now in terms of your question, Dr. Schroeter, and the representativeness of the survey, I think Dr. Mitchell has already commented on that. I don't think we agree that a priori one concludes that low enrollment per se necessarily means bias. It may mean bias. We will look very hard for that in other ways, as Dr. Mitchell outlined. We will be looking at other data bases.

Certainly it's easier to show there's no bias when your enrollment rates are higher, but I think that we don't agree that the low enrollment rate at the present time is necessarily indicative of absolute bias in the survey, and if it were obtaining a slice of the population, if you will, that are only the compliant. In fact, if you heard from Dr. Mitchell, we had two pregnancies so far in the 1,300 patients. That clearly is not a completely compliant population. I think Dr. Mitchell could comment further on it.

DR. MITCHELL: Let me just take a moment. I wanted

to respond to the figure of 6 percent that I heard. And I think that it's clearly a premature judgment based on 13 or 14 weeks of initial enrollment activity to extrapolate even the current enrollment numbers to a 6 percent annual rate. The problem with that is twofold. First of all, as you remember from that histogram the curve is clearly going up and we don't know just on the physician enrollment component what numbers we'll get. In addition, that's in the complete absence of the medication package enrollment program.

So that I think that we were trying to be careful to indicate that these were the most preliminary data, as any of you who have been involved with this kind of research would know, you don't make judgments based on 13 weeks of a pure start up.

DR. STADEL: I'll only comment back on that to emphasize that our judgment with regard to the study protocol is based upon the procedures of ad hoc peer review involving input of outside senior people in epidemiology and statistics.

DR. PENNEYS: Dr. Woodley?

DR. WOODLEY: I don't think people are disagreeing about the 60 to 70,000 new starts, but I may have misunderstood and some of the other people of the committee may have misunderstood Dr. Strauss' point that maybe that number wasn't wildly over usage of the drug. Could Dr. Strauss clarify what he said about that?

DR. STRAUSS: First of all, there are no good surveys that show you the true incidence of either nodular cystic acne. As far as I'm concerned, there are no good surveys that really show you the male, the female ratio of it. There's a lot of statements in the literature, but I don't think there's good data to back them.

What I said was that I thought that there was probably between 2 and 5 percent of the women who had acne who probably warrant treatment with this. I also said that there probably were somewhere between one-half and one patient per month that the average practicing dermatologist might need to put on Accutane. And using those figures which I think if you think about people who are in busy practices, and that figure was confirmed by talking with several people in practice who I respect and who I feel are not over prescribers. And they came up with even higher figures that we were somewhere in the range of maybe between 30 and 60 to 70 to 80,000, and those are very inaccurate.

I think that on the other hand the figure of 5,000 that has been used is way too low in terms of the total number of patients who do need treatment with this. And if you think about it and you think of your own practice, and then multiply that, that's saying that the average dermatologist does not have to treat more than one patient per year, and that is a ridiculously low figure, I think.

DR. PENNEYS: Dr. Stein?

DR. STEIN: I would like to ask if anyone knows of experience with a similar survey of medication usage which would give us a rate that we could hope for, a rate of enrollment that we could eventually hope for with this continual instincts?

DR. STADEL: To yield valid results?

DR. STEIN: I'm sorry.

DR. STADEL: I'm not sure I understand your question.

DR. STEIN: Is there any prior experience that would give us an idea of the percentage of enrollment that we expect with this survey of a similar circumstance?

DR. STADEL: To rely on it for its results, I would say in the range of 85 percent or greater participation. This is a mathematical consideration from this classification according to if those not participating are those likely to behave differently, one could work out some rather simple tables which support the notion. The unanimous perspective of those reviewing of this situation was that in order to validly estimate pregnancy rates and determination of outcomes thereof, the goals should be total ascertainment of exposure.

DR. STEIN: I'm not sure that I'm understanding you. Do I understand you to imply that eventually we can

hope for pretty high enrollment?

DR. STADEL: No, I'm saying in the present survey design, neither I nor those who have reviewed it considered there to be much of an appreciable likelihood that the enrollment rate would ever get to a level where one would feel comfortable, simply on prior considerations that the data would be a valid estimator of pregnancy rates for the population exposed as a whole, or that it would give you valid determination of pregnancy out rates after the exposure occurs. My point was that the recommendation of looking at the situation was that in order to handle the situation like this epidemiologically, the goals should be total ascertainment of exposure. That that is the design.

DR. PENNEYS: You're very critical about the study design and yet I heard very little criticisms from you about the previous designs in which incidence of cystic acne has been defined. You're basing your judgments on studies that are apparently much worse than this potential study.

DR. STADEL: I'm referring in the instance of this study to its likelihood of validity in measuring the pregnancy rate and the outcomes thereof with the study that is currently under development. When we comment on estimates of the problems and incidence, the one figure that was given I emphasize that it was based upon applying a variety of assumptions to the only population based data then available

or now available. There's a difference between trying to have some idea where you are, based upon what you have versus committing yourself to where you will be, based upon what you should be doing.

DR. SCHROETER: I understand the survey will be of great scientific help in establishing the rate of teratogenetic effects, however, how in the world is the survey going to reduce teratogenic effects? Why do the survey to reduce teratogenic effects? Is it going to reduce the number of teratogenic babies, effected babies?

DR. STADEL: My point here is first off is my concern in the orientation is on pregnancy exposure to the drug, because that is what is classified as a Category X drug. What happens after that pregnancy exposure is not the primary issue in the classification. It's whether the exposure occurs in the first place. Attendant upon that, the purpose of a post-marketing study in this context is to try to validly measure the rate of pregnancy exposure, so you can decide whether you think you're headed toward the goal of eliminating it.

DR. SCHROETER: There is no question that -- acid has a 100 percent teratogenic effects delivered or when the pregnancy is exposed. My question is how is the survey going to reduce the exposure?

DR. STADEL: The complete purpose of the survey is

to tell us whether the other efforts are in fact reducing the exposure. It's a feedback mechanism. As we've seen it in the discussions all along, you have a series of interventions aimed at accomplishing the role and then you must have a valid way measuring whether it's achieving that goal. The purpose of the survey of this kind of thing should be to provide a valid estimator or total measurement of pregnancy exposure.

DR. PENNEYS: Dr. Abel?

DR. ABEL: I just had one comment regarding the validity of the survey in regard to participation. And I don't see how it's impossible to predict at this point what the participation will be if its just recently been introduced with the blister pack. So that part, the patient enrollment or patient generated participation, we won't have an ideal of what that will be, so it could be quite high.

DR. STADEL: What I gave you was a peer review assessment based upon a lot of experience with studies that people with a lot of experience in this sort of thing think it extremely unlikely that what one would ever begin to approach a participation rate satisfactory for valid estimation.

VOICE: Could I add one comment on this question about what the likely enrollment would be after the blister packs are there. Most voluntary type surveys that have been

done rarely, if ever, achieve participation rates above about 20 or 25 percent. So I think that what we're facing here is almost the inevitable likelihood that enrollment will fall far short of the 85 to 90 percent that Dr. Stadel has been talking about to be necessary to provide a valid estimator of whether or not the interventions that have been put into place have achieved the objectives of the interventions themselves. And so I hope that sort of clarifies that for you.

DR. ABEL: I'm not aware of all the instruments that have been used in the past, but this can certainly be reinforced by the physicians. So although it's voluntary participation by the patient, being reinforced by the physician, I think the enrollment could likely to be quite much higher.

DR. PENNEYS: Response from Hoffman-LaRoche, please?

DR. MITCHELL: To answer Dr. Stein's question, if I understood it correctly, is no there is no experience upon which to base this. It's for that reason that we assemble the advisory committee. This is an unique undertaking. It is not before been attempted. The only vaguely comparable effort of which I'm aware was one mounted by Upjohn some years ago, Keith Gordon's group which in a targeted group of pharmacies was able to enroll as many as 50 percent of women---of the 50 percent of prescribed patients to certain

antibiotics, under very different circumstances.

We do not know what the participation rate will be. We cannot predict it. We would love to be able to predict it. We would be irresponsible to predict it. We don't choose to speculate on what that rate will be. There is another issue, and that issue is the distinction between representativeness and completeness. If one were to conduct the ideal and perfectly random survey and got complete information, it isn't necessary to get 100 percent of the enrolled population. So one has the obligation, as we've tried to describe it, to do two things. As one, to aim for completeness, by all means aim for completeness. And at the same time assess the representativeness to the best extent we can of the enrolled population.

DR. PENNEYS: Yes, Dr. Minus?

DR. MINUS: Can I suggest that we move the agenda. We are already one hour behind. We need time as a committee to discuss the various issues among ourselves and come up with some conclusions, and I just think that we should move on.

DR. PENNEYS: Is that agreeable with other members of the committee? All right. I'd like to ask the next speakers to try to limit their comments to 10 minutes. The first presentation is from the American Academy of Pediatrics by Dr. Roberts.

DR. ROBERTS: I am Dr. Robert Roberts. I am here to represent the American Academy of Pediatrics who have been quite concerned about this issue of Accutane for some time. It has prompted a number of discussions amongst our committees and the section on dermatology. There's been some agreement, some disagreements which prompted a task force meeting about a month ago to continue these discussions, so that the Academy of Pediatrics could come forth with a statement.

That task force represented the American College of Obstetricians and Gynecologists, the American Academy of Dermatology, Centers for Disease Control, and various segments of the Academy of Pediatrics, including the Committee on Adolescents, the Committee on Drugs of which I'm chairman, the Committee on Fetus and Newborn, and the Committee on Genetics, as well as a section member of the dermatology group. Consultation was also provided by the Food and Drug Administration and by Hoffman-LaRoche.

Now since this document has not been completed in its review, I'm going to have to summarize the findings of which the majority of members agreed. One is that Accutane is a efficacious drug for the treatment of severe recalcitrant cystic acne. And that Accutane is a potent teratogen and that this toxicity specifically is preventable. The precise criteria for diagnosis of resistant nodular cystic acne have not been developed, at least criteria upon which everyone

agrees. And because of the existence of teratology, the conclusion is that the drug is being excessively and inappropriately prescribed.

The recommendations include the urging of the membership of the Academy of Pediatrics to become more aware of the problem, that is, an effective educational program on the risks and benefits to Accutane. We're quite concerned about our adolescent group, and we're obviously quite concerned about the adverse outcome for fetus and for the newborn.

The Academy of Pediatrics should urge the FDA to establish a standing committee to more closely monitor and advise on drugs that are potential teratogens. This is not the first and it won't be the last, and there needs to be a standing activity structured to deal with this problem. We are very concerned about the collection of reliable, unbiased, and timely data regarding the issues surrounding teratogens, surrounding the issues regarding Accutane. . Without that data base it's very hard to come forth with a scholarly appraisal of anything.

It was our conclusion that the task force needs to reconvene at an appropriate time frame, the time is of the essence. Trends are ambiguous and we're skeptical of the impact of existing and proposed approaches to the problem with Accutane. And should there not be a data base that we

can reliably deal with and should the teratogenicity problem continue, that a recommendation should come forth from the Academy that a more restrictive scheme be devised for Accutane prescribing.

Conclusion--I'm done.

DR. PENNEYS: Are there any questions? How do you base your conclusion that Accutane is over prescribed? Based on what data?

DR. ROBERTS: If one accepts the fact that teratogenicity is unacceptable. I'm not an adverse witness here. I'm here to give you and share with you the concerns of the Academy of Pediatrics. And one is the teratogenesis is unacceptable.

DR. PENNEYS: Agreed.

DR. ROBERTS: And if it continues, then there's inappropriate prescribed.

DR. DRAKE: Has your Academy taken up other drugs that are teratogens? We heard some stuff from Dr. Hurwitz on dilantin, and I've not heard much from the FDA nor from the American Academy of Pediatrics. Have you in fact looked at other drugs that are potent teratogens that are more widely used, and in fact, produce more birth defects?

DR. ROBERTS: There are a number of statements that have been published by the Academy of Pediatrics in the past. Those are available in the Journal.

DR. PENNEYS: Any other comments? Thank you very much, Dr. Roberts. The next presentation is by Dr. Erickson from the Centers for Disease Control.

MR. ERICKSON: Good morning, almost good afternoon. I'm glad to be here to meet with you again to discuss the issue of birth defects caused by first trimester exposure to Accutane. I spoke before this group a year ago, and at that time I said much of what I'm going to say today. I view the repetition is necessary because I feel that over the past year, we've not made sufficient progress in controlling the reproductive problems associated with the use of Accutane.

I'm the chief of the CDC's birth defects and genetic diseases branch. Our mission is to search for causes of birth defects and to prevent unnecessary, morbidity and mortality due to these diseases. I was here a year ago, and I'm here again today because I believe the birth of babies with defects caused by Accutane exposure are unnecessary. Obviously if the drug were not available, these defects would not occur.

I believe that babies are still being born with Accutane embryopathy today and therefore I repeat what I said last year. It's time for a new and effective and more aggressive approach to preventing fetal exposures. Over the past year, the manufacturer has been active in developing and physician and patient education material, and in planning to

evaluate the effects of this educational effort. You've heard about these efforts this morning, and I think there's much to be praised here. But we believe that they will fall short of our goal of eliminating the birth of babies with Accutane embryopathy.

The approach to prevention that was taken in 1982, when the FDA decided to allow the marketing of Accutane was that of strong product labeling and a physician and patient education. The approach failed to prevent the birth of babies with birth defects. In fact, there seems to be evidence that the rate of fetal exposure did not decline to any marked degree after the renewed warnings in 1985. And we have no information available today to suggest that the pattern has changed over the past year, despite the very strong new warnings.

Well, because the problem could be markedly reduced by having better contraceptives available, we applaud the recent unanimous recommendation of the FDA's Fertility and Maternal Health Drugs Advisory Committee to approve Norplant, a very effective, long acting, implanting contraceptive. If the commissioner should act favorably on the recommendations, and we hope that he does, it will provide the potential to reduce the number of in utero exposures substantially.

We don't feel the problem will be fully solved by the availability of better contraceptives. Not all women

treated with Accutane will use them, and even though they could be very effective, they do fail occasionally. To approach a more nearly complete solution will require a restricted distribution to markedly reduce the number of fertile age women who use Accutane.

Why do we feel so strongly about this issue? It's simply a matter of our perception of the balance between risks and benefits. You all are well aware of the benefits of Accutane use, and perhaps you're becoming educated about the dangers based on some things that were shown this morning by Ms. Nygaard. In any case, it seems to me the balance is clearly not been weighted in favor of fetuses, in favor of those whose lives can be damaged or destroyed by exposure to the drug.

This committee should explicitly address the difficult issue of equity and make an accounting of the risks and benefits of Accutane use and to balance the interests of those--the benefits that accrue to those who have skin problems, with the damage that's done to babies. I think you need to advise the commissioner on how many persons cured of severe cystic acne is a fair and equitable balance for each baby born with a serious physical and/or mental deficit.

If I could have the first slide, please. I want to share with you some estimates that we have made that will help push this issue of equity into concrete terms. This

graph shows our estimates of the number of babies that would be effected by Accutane and embryopathy for varying numbers of drug users. We present estimated effected numbers for three different contraceptive failure rates--20 percent, 3 percent which is the typical OC failure rate, and 0.3 percent which is the approximate failure rate of a preparation like Norplant, the implantable that has recently been recommended for approval.

If I could have the next slide, please. I made a number of assumptions in arriving at these estimates. First, that all courses of treatment are five months long. Two, that one-third of fertile aged women 15 to 44 years are non-fertile or sub-fertile, and 14 percent are not sexually active. That the remainder are sexually active and have fertility rates equal to the various contraceptive failure rates, that is, 20 percent, 3 percent, and 0.3 percent. That no treatments will be started before ruling out pregnancy. That about 50 percent of women who have an exposure during pregnancy will elect to terminate the pregnancy. And that we have a fetal death rate of about 20 percent, which may be judged to be too low. The fetal death rate may be double that. And lastly, that about 25 percent of babies who fetuses that have reached term will have malformations.

May I have the next slide, please. Well, it's obvious that a marked reduction in the number of babies born

with Accutane embryopathy with malformations caused by Accutane could be reduced by reducing the number of women who use the drug. I've included the number 4,000, and we would expect somewhere between 0 and 12, depending on the mix of contraceptive use among those 4,000 women. I present the figure for 4,000 users because that's the number of fertile aged severe cystic acne cases made last year by Dr. Graham.

We present data for numbers up to 70,000 users which is the approximate number of current users, as you've heard this morning. At this level of use, we can expect somewhere between three and a couple of hundred babies born with malformations caused by Accutane. Again, depending on the mix of contraceptive methods used. I emphasize that the number three for 70,000 users would be an ideal with a highly effective long-acting contraceptive available. That promise does not pertain today because they are not available in this country.

Well, I still think that a restrictive distribution system to reduce the number of users is also needed. A decision to depend on better contraceptive alone without active intervention to reduce the number of users is a decision to leave the number of effected babies at a level which to me is unacceptably high.

If we could just talk a little bit about this issue of the long-acting implantable and injecting contraceptives.

They are viewed as a method for women who have completed their desired childbearing, a good method for them to control their fertility. The use of the implantable contraceptive which is on the docket now, requires a minor surgical procedure to implant and another one to remove. So we wonder what proportion of Accutane users would avail themselves of that preparation, particularly teenagers, if the use was not made mandatory, along with prescription of Accutane.

Last year I described an example of a restrictive distribution scheme for teratogenic drug in the United States, that is, the investigational new drug application use for the distribution of thalidomide. Perhaps a formal IND sponsored by the FDA would be a suitable mechanism for helping to reduce the frequency of Accutane embryopathy. But seems equally likely that the voluntary restriction by the manufacturer potentially could be as effective as IND. And as I understand it, there's precedent for voluntary restriction in synthetic growth hormone and for some chemotherapeutic agents.

If I could have the next slide, please, and I will again describe to you CDC's ideas of what would be an acceptable limited distribution plan that would make Accutane available to all persons in need of the drug, including potentially fertile women. And we think this could be done as a result of FDA action or as a voluntary action on the

part of the manufacturer. The plan we think should include is a minimum that the distribution would take place through a limited number of institutionally based centers and that these centers would be responsible for seeing the protocol is followed by prescribing physicians.

We are certainly not experts in how to design such a system, let me say that, I was struck by several remarks this morning that people might have to travel all the way across Iowa or across Georgia to a center to get the drug. CDC has quite a number of IND's for drugs for rare tropical diseases, and we do not fly people into Atlanta for treatment. Physicians who feel their patients need the drug cooperate with CDC, and, in fact, become cooperating investigators on the IND. It seems to me that the issue of travel and those sorts of access problems should not deter anyone from instituting distribution by the institutionally based centers.

Our center view committee would require certification by the physician wishing to use the drug for a particular patient, that the patient has severe acne that is resistant to other forms of treatment. The manufacturer in cooperation with the centers would device innovative approaches to educating professional who want to prescribe Accutane, educational approaches about the dangers of the drug, and about the facts of contraception.

There would be a center oversight procedure that

would require certification that women who are treated are of minimal risk of becoming pregnant during and shortly after treatment. Ideally the physician prescribing Accutane would coordinate the use with another physician who would be helping the woman manage an effective method of contraception. Prescriptions would be limited to one-month's supplies of the drug. To receive continuing treatment, the patient would need to return to her physician to have a reliable pregnancy test performed. The system would be designed that women should return at an appropriate time after the completion of treatment for a final pregnancy test.

The goal of all of this from our point of view is to prevent fetal exposures, but failures will occur, and each center should have some sort of assistant for ensuring that women receive adequate counseling. Some women may elect to continue their pregnancies, while some may elect to have induced abortions. Induced abortion is an intervention which has been used in Accutane exposed pregnancies and will continue to be used, so long as Accutane is available for use by fertile women.

Again, I emphasize a preferred course of action is the prevention of female exposure. And lastly, we believe there needs to be an evaluation of the prevention strategy, ideally including a national registry of patients who have exposures during pregnancy with a follow-up of pregnancy outcomes

We have heard much talk in the last hour about difficulties in devising a follow-up system on the restricted marketing approach that we would recommend would make follow-up feasible and without this sort of an environment evaluation to follow be very difficult.

That concludes my presentation. Thank you again for the opportunity to be here to speak with you. I will be glad to field questions.

DR. PENNEYS: Thank you, Dr. Erickson.

Are there any comments or questions? Dr. Drake?

DR. DRAKE: On your first slide, you have a slide of assumptions that you made. Can you tell me your data base for your assumptions and the literature from which it came?

DR. ERICKSON: Well, I could briefly go over that, if you like. I could put that--I would say they are--

DR. DRAKE: Actually, in order to conserve time, I would be happy to have you send it to all members of the panel.

DR. ERICKSON: Okay.

DR. DRAKE: I think some of those assumptions, I don't have any idea where they came from, but it would help if we had the literature--

DR. ERICKSON: I understand.

DR. DRAKE: --and the data base from where they came.

MR. ERICKSON: Absolutely, I would be glad to do that.

DR. PENNEYS: Any other comments?

[No response.]

If not, the next presentation is by Dr. Sidney Wolfe, from the Health Research Group.

DR. WOLFE: The work for this presentation was done with Dr. Andrew Holmes, who is a pediatrician spending six months with the Health Research Group. He will give copies of the longer statement and I will just spend a little less than 10 minutes of the allotted time.

One year ago, in the disastrous wake of 62 life-threatening or severaly developing birth defects which had then been reported in babies in the United States whose mothers has been exposed to Accutane during their pregnancy, in addition to hundreds, if not thousands of abortions, spontaneous or induced, in women similarly exposed, we testified before this Committee, and on May 17, 1988, petitioned FDA to much more tightly restricted use of Accutane in order to prevent these tragic occurrences. Our petition also included a number of changes in labeling and other things which the company and the FDA agreed with, and I would say that outside of the area of restricting the use, that the company has done a very commendable job. We just don't think that it is enough.

This Advisory Committee at the meeting last year was predictably very concerned about the fact that Accutane was still being widely prescribed to women of child-bearing

age and that exposure of large numbers of pregnant women to the drug was still occurring. Although the Committee left the details of what to do to the FDA, you voted that distribution should be limited or restricted amongst the possible ways of doing it, including restricting it against use by women of child-bearing age, restriction on the actual distribution of this drug, as by doctors, restriction to special physicians distributing the drug, restriction of special patients who get the drug, and necessity of a second opinion.

I think in good faith you have said, FDA, you have got to do something or other in the way of restricting.

On May 2nd, last week, FDA rejected those parts of our petition which would have limited prescribing to those dermatologists who had signed a written statement that they would only prescribe Accutane for those women with severe cystic acne, not responsive to other treatments, and would agree to perform an initial pregnancy test to rule out pregnancy, as well as periodic pregnancy tests, to assure that women not pregnant when starting on Accutane did not subsequently become pregnant. Criminal penalties would have resulted if doctors violated this agreement. The reason for that is this is a serious problem and it requires serious solutions.

The FDA conceded that it may have the legal authority to adopt our recommendations, but refused to use this

stating, in the words of FDA Commissioner Frank Young, that this "would constitute an unprecedented intrusion into the doctor-patient relationship." We would argue that it is time for this kind of intrusion to occur, given what appears to be very little evidence of decreased use by women of child-bearing age.

In the year that has elapsed since the last hearing on this topic, irresponsible actions by Roche, the failure to, as Dr. Erickson just suggested, voluntarily restrict the distribution, and inadequate action by top FDA officials--emphasizing that, because I think that at most other levels in the FDA there is definitely a consensus that there should be a restriction--have resulted in the continued high rates of doctors prescribing Accutane to women of child-bearing age without any credible evidence that the number of Accutane caused birth defects or abortions has decreased.

I will skip over at least a lot of the data analysis because it has been presented both by Roche and later by Dr. Stadel, but I think that the summary of it would be that there really is not any good, reliable evidence of a significant decrease in new starts or new prescriptions, the important category of prescribing, because this is where the pregnancy is most likely to occur.

Skipping to page 3, the status quo: One, there has been a singular lack of progress on the part of Roche since

this time last year. The blister packs were not available as of a week or so ago. They are available now. There is not yet any adequate post marketing surveillance. Roche has conspiruously flouted the FDA directive by proceeding with the protocol of marketing surveillance that was rejected by the FDA and its advisors.

The promulgated of biased data gathering is tantamount to a disinformation campaign. I would suggest that if anyone ever took a protocol like this and tried to get funding from the National Institutes of Health, the National Center for Health Statistics, that it would be rejected. I agree with the estimates that you need to have 80, 85, if not 100 percent follow-up, and I would bet that it is very unlikely that we will get more than 20 or 25 percent. Even at the rate the last couple of weeks, which was about 100 new recruitments a week, that would project out to 5,000-some a year, around 10 percent. I think it is going to be higher than that, but perhaps not much more. I would bet that it will exceed 20 percent, and I don't think anyone would agree that that is the best kind of data to use.

The people who are involved in doing this study are amongst the best epidemiologists in the country, and if they had their druthers, they would have a registered release and most of them have stated so, and this is included in internal FDA memos which have been made available to us.

The FDA has, in a partial denial of our petition, brought into Roche's obstructive strategy by referring to the study--the surveys is what it really is--without mention of the flawed protocol and the jus-ification of its decision. In Dr. Young's May 2, 1989, letter to us, he stated that, "A survey is being conducted by Hoffman-LaRoche to identify the rate of pregnancy exposure among women prescribed Accutane to help the agency determine the effectiveness of the total intervention programs undertaken to date."

Despite Dr. Young's embracing of the Roche-funded study, the protocol for this survey was rejected by FDA scientists after review by its Epidemiology Unit and by two independent reviewers, Dr. James Schlesselman of the Uniformed Services University, and Dr. Barbara Hulka of the University of North Carolina.

The basis for rejecting the protocol was that, since it was not going to include a large portion and representative sample of women using Accutane because of its voluntary nature, the results would be biased. I won't go into more of that. There has been a discussion already this morning of that.

Dr. Shapiro, of the Slone Epidemiology Unit said that he expressed the opinion that registered release would produce the best study. The idea of registered release of all Accutane prescribing is also supported by a FDA epidemiologists and other scientists and outside FDA consultants as the best

way to find out what is actually occurring in women who are receiving Accutane.

I stress that there is a connection between the distribution of the drug, a restricted distribution, a registered distribution, and the ability to do the proper kind of study. You need both of them together, otherwise it is sort of a Catch 22, without some registered restricted release you do not have anywhere near the kind of follow-up you will need to ascertain the impact of the other kinds of interventions.

Moving on to page 5, Conclusion 1, there has been no demonstration that the interventions since the last Advisory Committee have been adequate to address the extremely serious problems associated with Accutane.

Two, the rate of Accutane prescribing does not appear to change significantly. Most importantly, first-time Accutane use by women of child-bearing age has not declined from the levels of three years ago. A year from now, we are not going to know if pregnancy exposures have been reduced, because we do not have an adequate data collection system. As it stands, we will have no way of knowing whether the blister packs actually work to reduce pregnancy exposure. Our only reasonable information is prescription numbers and blister packs are a post prescribing intervention.

Four, focusing on the number of birth defects evades the issue of the number of spontaneous and induced abortions

consequent to Accutane exposure. Abortion should not be regarded as a satisfactory outcome for pregnancies exposed to Accutane, even though it will relieve the company of some product liability lawsuits.

Five, we should not lose sight of the fact that there are other major morbidity associated with Accutane use which have been referred to this morning. We are frequently getting phone calls from people who had other serious side effects.

Six, responsibility for adverse outcomes from Accutane use has been shifted from Roche, the manufacturer and marketer to the prescriber and patient. This isn't a phase of Roche being obstructive to the process of gathering post marketing data and misleading the public in its product warnings. Again, I refer to the fact that, even though the FDA has not used the legal authority that it does not deny it has, the company could engage in restricted distribution and it would thereby have a much better kind of surveillance system to use.

What do we do? One, there must be immediate restrictions to reduce Accutane prescribing to severe acne that does not respond to more benign therapy. Our petition outlines a workable set of such restrictions. Although FDA rejected that part of our petition which would impose these restrictions, the agency does not deny that it has the legal

authority to implement these mugh tighter restrictions.

It is interesting that in one year the agency does not seem at the legal end or at the top end to be able to come up with a decision as to whether they have legal authority and they sort of leave you all in limbo. I think that your conclusion last year that some restriction should be done was based on the assumption that FDA might at least have the legal authority. I think it is inexcuable that as to now they one the one hand don't say that they don't have the legal authority, and on the other hand they don't say that they do.

If they don't have the legal authority, we want to hear about it, because there is a lot of interest in Congress in quickly passing legislation that would give them the legal authority to do the restricted distribution and thereby be able to do a proper kind of surveillance.

Post marketing surveillance with rigorous 100 percent follow-up should be made an immediate requirement by FDA. The protocol should be submitted to and approved by the FDA, in consultation with independent reviewers. If the FDA finds that it doesn't have the legal authorities, as I just said, Congress will give it the legal authority, I will bet.

Three, upon future review of Accutane use, its continued availability should be contingent on hard evidence that it is being used appropriately and with a clear major reduction in drug-related morbidity. For product warnings to

physicians regarding the outcome of pregnancy following Accutane exposure should include the actual measure relative risk of Accutane-induced birth defects. Information should also be provided about the effects of dose gestation time and duration of exposure and pregnancy outcome.

Finally, this is an administration which claims to be strongly against the rights of women to have an abortion, if they choose to. It is especially ironic that FDA negligence at the top level has resulted in massive and continued prescribing of a drug to women of child-bearing age which is predictably causing birth defects and, in the more frequent scenario, the FDA is implicitly recommending that most women who use the drug while pregnant should have an abortion.

By refusing to require Roche to state more accurately that serious birth defects occur "in one chance in four or greater" of fetuses exposed to Accutane during pregnancy, as FDA stated a year ago in a talk paper, it instead is allowing Roche's labeling and patient warnings to state that "potentially all exposed fetuses can be affected" by the severe birth defects.

FDA Commissioner Frank Young is allowing women to be misled into believing that the odds may be almost 100 percent that a serious birth defect will occur, thus increasing the likelihood that they will choose an abortion. A 1983 memo from Dr. Lammer, then at the CDC, in response to a

conversation with some from Roche, suggested that Roche's strategy was to put out the assumption that there was 100 percent birth defects and that implicitly abortion should be recommended.

In summary, the failure of Roche and its partner, FDA, to more severely restrict the use of Accutane, the failure to initiate or impliment acceptable surveillance to determine the current extent of pregnancy exposure and the failure to accurately inform women, those women who become pregnant while using Accutane, the actual chances of a major birth defect must be shown by your Advisory Committee and the Fertility and Maternal Health Advisory Committee, which will review this issue on June 2nd.

It is our position that unless FDA immediately imposes the restrictions on Accutane prescribing which we outlined in our petition one year ago and puts in place an effective monitoring system to track pregnancy exposures and outcomes, such as abortions and birth defects, Accutane should be immediately removed from the market.

Given that the epidemic of Accutane caused birth defects and spontaneous and induced abortions is the worst such drug induced epidemic to occur in this country, it is time for FDA to require an "unprecedented intrusion into the doctor-patient relationship" to protect the tens of thousands of American women of child-bearing age who are still

prescribed Accutane.

Thank you. I just included in the end in a little more detail a chronology of what has happened since 1954 when Vitamin A was shown to cause birth defects. I would be glad to try and answer any questions.

DR. PENNEYS: Dr. Woodley?

DR. WOODLEY: I was just wondering about conclusion number six, why your group does not feel that the responsibility for the drug in some part, in some measure should not be upon an informed physician and an informed patient. I mean we--

DR. WOLFE: I do. I was simply--I think that we always have to have responsible physicians and patients. What I really was saying is that from a legal or product liability or litigation standpoint, there is no question that the burden is shifted to the doctor and the patient. In the future, unless someone shows, as they might, that Roche was negligent in not restricting the use of the drug to certain physicians, only if they agree to do certain things, what may have been five or six years ago a product liability suit against Roche will be a malpractice suit against the practitioner. That is really all I was meaning. I did not mean to imply that patients and doctors don't have to have responsibility.

DR. WOODLEY: Maybe this was the wrong analogy, but

I read yesterday that GM is coming out with a new Corvette that goes 180 miles per hour, but we give that Corvette to anyone who wants to buy it, knowing that there are going to be 60,000 accidents and eaths on our highways every year. So, ultimately doesn't our society say that it is the individual, the informed individual that has some responsibility for their own behavior, and it is not the company or it is not a super-structure of the government?

DR. WOLFE: Well, I think that, yes, informed individuals probably play an important role. But the fact that you have spent the hundreds, if not thousands of hours you have spent on the Advisory Committee of the FDA, I think suggests that you believe that there is a role for government intervention.

I think what we are saying here now--and I agree with the definition before, the definition of over-prescribing or mis-prescribing or inattentive prescribing is the continued existence of birth defects and spontaneous or induced abortion. I think that any reasonable--and I emphasize reasonable--intervention that can be imposed by the company itself, which it chose not to so far, or the FDA by way of restricting the use so that we get the benefits and minimize the risks.

I think that the chart that Dr. Erickson just showed on what various kinds of effectiveness of contraception would do to the number of birth defects or, conversely, the number

of spontaneous or induced abortions at various levels of prescribing suggests some ways of changing things. I agree that, even though we don't have the best kind of epidemiologic evidence as to exactly what the target population is, I think it is probable, at least the dermatologists I have talked to who are careful and who prescribe this drug very, very rarely, all know dermatologists who over-prescribe the drug. All of you know such dermatologists, and it is not I think so much for you and people who practice as you, but people who practice excessively.

DR. PENNEYS: Dr. Wolfe, can we restrict our discussion to data or our analysis to data.

Any other questions?

[No response.]

I have one comment, and that is for the record. The vote on restriction at this meeting last year was tied.

DR. WOLFE: It was 4 to 3, as I remember.

DR. PENNEYS: Well, you are incorrect, and the minutes are here and available for your study, if you wish.

DR. WOLFE: The Chairperson didn't agree? I mean there was a comment made on these various kinds of restrictions that--

DR. PENNEYS: Dr. Wolfe, they are a matter of public record here and you have access to them.

DR. WOLFE: Well, let's assume that it was tied,

then thatmeans equal numbers of people--

DR. PENNEYS: I am not arguing the point. I am just for the record correcting you and saying that it was a tie vote.

DR. WOLFE: Well, I would hope you would change your mind and vote in foavr of restriction this year, if that was the case.

DR. PENNEYS: Thank you very much.

Why don't we move on to the next presentation by Dr. Lammer, who is from the California Birth Defects Registry.

Dr. Lammer, the Committee would really appreciate it if you could try to do this as quickly as possible.

DR. LAMMER: I am pleased to be here to talk to the Committee again this year, after inviting myself to come for the second year in a row.

Again, I agree with many of the previous speakers, I don't think this is a problem that has gone away or disappeared over the past year, and I want to present some data hopefully that will shed a little bit of light on some of the questionsmarks that were before this Committee lastyear, for which I think we have a little bit of data to answer a couple of questions, but certainly not all of them.

[Slide.]

This is a slide showing to the best of my knowledge the number of cases by year, this is children who have at

least one major birth defect. This is limited to patients in the United States, excludes the cases from Canada, and these are only the major birth defects in pregnancies reaching 20 weeks or beyond. Now I understand that Hoffman-LaRoche is aware of 2 infants borth in 1989, and since we made this slide now I need to update this. We now have identified 10 children born in 1987, so that the curve for these 4 years is relatively flat and, again, we are just into 1989 and there are only 2 cases that have apparently been identified as of this year.

Now, for the members of the Committee who weren't here last year, I just want to briefly review the studies that we do. We are involved, to the best of my knowledge, in the only longitudinal study of the outcomes of pregnancies exposed to Accutane, even in the first or second trimester of pregnancy.

We basically studied two populations of children. One is this prospectively followed cohort, that is, we follow pregnancies that are identified to us in which women have taken Accutane, and to be eligible for this cohort, the pregnancies have to be identified to one of these sources, Hoffman-LaRoche, FDA, CDC, or our study group, before there is any knowledge of the outcome of the pregnancy, that is, before any ultrasound procedures have been done, and certainly before the welfare of the fetus or embryo have been established.

So, by following the outcomes of this group, it

gives us an unbiased spectrum of the whole range of possible outcomes. The other group that we study--and this is important to differentiate the groups--is a retrospectively identified case series of children, all of whom have major birth defects. That group is primarily valuable for giving us some idea of the severe end of the spectrum of effects and to give us some ideas about the possible mechanism of action, whereas this prospective cohort, as I said, gives us a picture of the full spectrum of effects and in what we think is an unbiased fashion.

Now, you have heard some previous slides showing that in fact the number of exposed pregnancies has not decreased significantly since 1985, and our data is certainly supportive of that. These are pregnancies we have identified prospectively. Again, these numbers have changed since I made the slide.

There are now in 1985 12, 8 in 1986, 7 in 1987, so the curve should pretty much be flat--12 in 1988, and we have already identified prospectively 5 pregnancies, 2 of which have delivered this year, 3 of the women still have not delivered their babies yet, so still we are only at May 1st. Our vision, in terms of pregnancies that we have identified prospectively as being exposed is flat, with a little bit of bump, in fact, in 1988.

Now, we certainly haven't seen a decreasing trend,

and I should note that there has been one significant change in the types of pregnancies that are identified to us. If we look at the pregnancies we have ascertained in this fashion since 1987, in fact, nearly all of them are exposures which are limited to the first 14 days after conception, so we have seen a change in the types of pregnancies that are referred to us, and I have interpreted that as consistent with the idea that women with exposures that extend farther into pregnancy are getting counseling and that there is a high risk of teratogenic effects and are terminating those pregnancies and they neve get referred to us. Whereas, pregnancies in which the exposure is limited to the first several weeks after conception, there are still a lot of questionmarks about whether the magnitude of the risks are lower during that period, and so the groups who refer patients to us, like genetic counselors and obstetricians, are more likely to contact me to get information about the magnitude of risk for exposures in that period.

So, that may also explain why we haven't identified any malformed fetuses in 1989, because the epidemiologic characteristic in terms of timing of exposure that we are seeing in the patients we ascertain has changed over the last couple of years.

And just for the purposes of informing the new members of the Committee, basically the results from following

the first 61 exposed pregnancies, we find for pregnancies we identified or we ascertained before 13 weeks after the LMP's, i.e., the first trimester, we find a 40 percent absolute risk for spontaneous abortion, and we would regard this as a minimal estimate. It is likely to be higher than that.

Again, of these first 61 pregnancies we followed prospectively, in the green area are those which reached 20 weeks gestation and beyond, 11 out of 47 or 25 percent of these babies were born with at least one major birth defect.

Now, at last year's meeting there was a lot of debate about the need for getting some better estimates about the number of affected children and spontaneous abortions that may have occurred nationally, so we made an attempt to look at our data in that regard, and this is a little bit tricky to follow, so I will try to go slow, despite the Chairman's admonition that I speed this up.

Now, two differences we have observed between the prospectively followed cohort of pregnancies and those retrospectively identified malformed children that I think can shed some light on estimating the number of affected children or fetuses that are, and those two factors are, one, in the prospective cohort the types of malformations those children have tend to be less severe than those we identify retrospectively, and they are much less likely to include irreparable congenital heart defects. So, that the pattern of malformation in

this group, even among those with major malformations, is milder and less severe than those in this group.

The other factor which is consistent with that is that of the 11 malformed from the prospective cohort, the mortality is 2 out of 11 or, rounded off, is, say, 20 percent, whereas, retrospectively identified pregnancies, the mortality is between 60 and 70 percent. So, that differential mortality suggests that even among the severely malformed--I'm sorry, even among those with major malformations identified prospectively, their abnormalities are less severe than this group, suggesting that there are a number of children with major malformations less severe than this group who have not been identified yet, and this is the premise for the estimate that we came up with.

Now, basically, in our prospective cohort it breaks down like this: 40 percent of the pregnancies have spontaneous abortion, and of those that don't abort, 15 percent of the overall 100 percent group have major malformations.

Now, within that group we find about a 20 percent mortality. Now, if you compare that to the retrospectively followed group, again, I use the number 74 here because it was my understanding that the FDA had ascertained a total of 85 malformed children, and then when we subtract the 11 from this group, I came up with 74. This number actually may be somewhat lower, but you can revise our estimates down a little bit

if you assume that the total number that have been reported to FDA is actually smaller than this, again, in this group a differential mortality of 60 percent.

The assumption we are making here is that the two groups, the sub-groups of this group of patients who are most comparable to this group are the 20 percent of the malformed who have died, compared to those who have died from the retrospective case series, and I hope you are able to follow that logic.

So, what we are saying is that our prospective cohort, the mortality experience among those malformed is 20 percent, and that is 2 of 11, so that is the weak part of this data. And then in the universe of malformed infants in the United States, if the mortality experience there is 20 percent, we then estimate that the total number of affected that that comes from is a universe of 220 malformed infants, so this number 44 is 60 percent of the 74 malformations identified retrospectively to the FDA. So, of those identified to the FDA, 60 percent or 44 have died, and we are guessing that that 44 is 20 percent as a universe of malformed infants that we estimate is approximately in the range of 220.

Now, extrapolating from those numbers, if this is the percentage of abnormalities of exposures that we identify prospectively, that is, 40 percent of the pregnancies abort and 15 percent of the universe of exposed end up in a malformed

child, then our minimal estimates would be 230 malformed infants and 613 spontaneous abortions. Now, not all of these are going to be attributable to exposure, so if you assume that for recognized pregnancies, the background risk for spontaneous abortion is 15 to 20 percent, that means of this number, approximately this number would be attributable to exposure, whereas, nearly all of the malformed infants are going to be attributable to the exposure, leaving us with this question-mark in terms of the number of children who do not have malformations but who will, nonetheless, end up with some kind of developmental disability as a result of the exposure to the drug.

Now, next I want to talk about the second phase of our study which we just started in October. The purposes of this study--and this is supported by Hoffman-LaRoche on a grant to the Massachusetts General Hospital--is to quantify the risks for developmental problems at age 5 years among malformed that are apparently non-malformed exposed infants, and we are looking at these outcomes, behavior, intelligence and socialization, and we are primarily interested in seeing what kind of problems the children are having who don't have major birth defects, and these are the measures we look at--I.Q., with the WPPSI Vineland Social Maturity Scale, vocabulary, off-the-floor kindergarten battery, and these other assessments of memory, motor coordination, perceptual motor

functioning, attention deficits, and behavioral problems, and this work is being done in collaboration with Dr. Jane Adams, who is performing most of the developmental testa, and I want to present some of our very preliminary results which I just saw for the first time this morning on some of the developmental outcomes in the first 20 infants we have evaluated at 5 years of age.

Now, these 20 are all unbiased. This is from our prospective cohort, so some of these children have major malformations, and some of them don't, in fact most of them don't. I think only 3 or 4 out of this group of 20 have major abnormalities, and basically what we are finding--and again, I want to stress, this is preliminary, this is based on the first 20 --40 percent of these children have an I.Q. below 85, which Dr. Adams suggests to me is an I.Q. range for which a child would unlikely be able to function well in a normal classroom.

Specifically, the most common abnormality that we are seeing is problems with visual motor integration, primarily manifested by picture-naming ability and other tests. This is a test that assesses a child's ability to integrate information that they receive visually and is the sort of problem that children have who will eventually have difficulty with reading and writing and learning from material that they receive from a visual source.

Lastly, one of the questions that came before the

Committee a year ago was the question about whether the teratogenic effects might be reduced by lowering the recommended therapeutic dose for the medication, and I think in the last year a lot of new information concerning this issue has come out and I want to present this case report which we have in press currently.

This is a mother who was taking 40 milligrams of Accutane a day. She took it from day 8 to day 28, with day of conception being day 0. On day 31, that is about 72 to 80 hours after the last dose, she had pregnancy termination. At the time of the termination, we drew simultaneously blood, her blood, and measured both Accutane levels and metabolytes of the drug.

From the products of the termination, this was work done, we sent the samples to Hines-Nows Laboratory in Berlin, we were able to find a .2 gram intact 31-day human embryo and were able to measure levels of Accutane and its metabolytes both in the embryo tissue, placental tissues and maternal serum simultaneously.

Now, the results--I want to run you through this because I think it is pertinent to decisions made by this Committee--in the mother's blood, we find levels of Accutane in the primary metabolyte the 4-oxo compound to be just what you would expect for a blood sample taken about 3 days after the last dose, that is, the metabolyte is present in the

higher concentration in the parent compound, and all trans-retinoic acid present in about the same concentration as to Accutane.

Whereas in the embryo tissue, the absolute numbers aren't important here to relative ratios, what you see is in fact the Accutane level in the embryo is much higher than the metabolyte, and that in fact all trans-retinoic acid is present in an extremely high concentration in embryo tissue also.

What we see in the placenta is a similar phenomena, that is, in some areas of the placenta we see concentrating of Accutane, whereas we don't see increased levels of the metabolyte, the opposite situation of what you are seeing in the meternal blood. But the picture in the placenta is a little bit confusing, because it is apparent that there is regional concentrating of both Accutane and all trans-retinoic acid is not a uniform process throughout the placenta.

Since we disseminated this information, several laboratories have basically documented that this is apparently also the case in experimental animal species, that Accutane and all trans-retinoic acid, it seems concentrated in the placenta and embryonic tissue relative to the concentration of the drug and the all-trans in the maternal blood, and we think this is consistent with several possibilities.

One is that the drug is isomerized, may be isomerized in the placenta or in the embyro from the 13 cyst to all trans-retinoic acid, which is much more teratogenic compound, or that the drug is simply being concentrated in placenta or embryo tissue through some process that is not clear at this time, so there is a lot of work to be done on this. But the reason I am presenting this information to your Committee is that, based on what we are learning now that there is an isomerization reaction and that a more teratogenic compound is being generated and that the drug is concentrated in embryonic and placental tissues, it makes it unlikely that a strategy of recommending a lower therapeutic dose would be effective in reducing risks for teratogenicity.

Lastly, I would just like to say that I must concur with what Dr. Wolfe said, in that my recollection of the hearing of a year ago was that the Committee, although the vote was 3 to 3 to recommend a restricted distribution plan, in fact that was endorsed by the Chairman as the fourth vote.

In my correspondence with the FDA, I have not seen any kind of a disavowel of that voting. Now, my feeling is that a year ago the Committee did vote to recommend a restricted distribution plan, and in fact several members of this Committee at that time, in their deliberations, mentioned that they were only in favor of some of the recommendations which have been enacted by the manufacturer if there was a

restricted distribution plan developed with those other recommendations.

Now, for reasons that aren't clear to me, the FDA and Hoffman-LaRoche have decided not to implement a restricted distribution plan. My own feeling is that I hope the current changes will work, but I am quite skeptical that they will, and I would like the Committee to go back over the issues related to a restricted distribution plan, because I think this has the greatest potential for bringing about a resolution to this problem, and I would be happy to answer any other questions or if I can be of any help.

DR. PENNEYS: Are there any questions?

[No response.]

Thank you, Dr. Lammer.

Now we will go on to the last presentation by Dr. Jansen, from the American Academy of Dermatology.

DR. JANSEN: Chairman Penneys, Dr. Roubein, I appreciate the kind invitation for dermatology to again be represented here. I am Tom Jansen, Immediate Past President of the American Academy of Dermatology, and I was at the hearing on October 26, last year.

As a physician practicing private dermatology in Little Rock, Arkansas, for the past 33 years, I have seen many patients with severe nodular cystic acne, and I trust that those patients that I have treated effectively with this

almost miraculous drug are also being represented by me at this time.

Severe cystic acne produces profound permanent scarring that you have seen, and I have deleted the slides from my presentation because I think you all appreciate that this is not a nonchalant incomplete disease, but really one that is quite destructive.

In spite of the fact that many treatments were used by me and others, either singly or in combination, none of these treatments proved to be completely effective. In fact, some of them produced very dramatic side effects and it was not uncommon for me to use very high doses of Vitamin A at the 100,000-200,000 unit level, and I would point out to you that such dosages can be taken at this time by patients through over-the-counter purchases if they wish to.

Dermatologists know that there are not alternate effecrive treatments for cystic acne at this time, except for isotretinoin, and I would also point out that this disease does not limit itself to the adolescent period. but really continues through adult life and that it is a significant disease for these people year after year after year, without the benefits of isotretinoin.

In spite of these concerns, the members of the American Academy of Dermatology, experts who knows this disease, its natural history and the ineffectiveness of these

alternate therapies conclude that the benefit-risk ratio, referred to at this meeting ealier, justifies its present and continued use with appropriate warnings and protection against pregnancy during therapy.

Those of us who are aware of the investigative work in related compounds in the retinoids are fearful that the research that is going on or the possible benefit in even much more important diseases than cystic acne would be lost should there be severe restrictions on this compound at this time.

In May of 1988, immediately after the hearing last year, I as President of the Academy mailed a "dear colleague" letter to the entire AAD membership, reporting on your deliberations, discussing FDA concerns, and announcing the appointment of a committee to develop guidelines for the use of isotretinoin. These guidelines were immediately developed and approved by our board of the American Academy of Dermatology in early June of last year, and some were available at the registered counter.

Just prior to the approval, the FDA formally requested the participation of the Academy in a broad education program to inform physicians and patients as to the potential hazards and benefits of Accutane, and I feel that our stewardship would indicate that we have carried this out. We willingly undertook to inform our members and included in out Journal in July 1988, the Journal of the American Academy of

Dermatology, much information concerning Accutane, its dangers and the guidelines that I have previously mentioned.

Withdrawal of isotretinoin from the market would force us to deal with young people who are physically and emotionally ravaged by this disease, as indicated by Dr. Hurwitz, and scarred for life. This would be unfair to all patients suffering from severe cystic acne, but particularly unfair to the 70 percent of those for whom the drug is prescribed, men and women who cannot bear children.

On the other hand, to have a completely restrictive system of use, as was proposed, including the type of distribution for Thalidomide, would be equally unfair restrictive for those same people who can now take the drug without fear of pregnancy.

So, in your deliberations on a restricted program, it would certainly be hopeful, from the standpoint of the American Academy of Dermatology, that those restrictions would not pertain to those people who do not have these fears.

Again, I as a representative of the American Academy of Dermatology, would like to thank the Committee for listening to us. We are eager to join in any programs that you feel are appropriate, and I would stress that dermatologists are sensitive to the issues being raised at the present time as they relate to birth defects, and the Academy will continue to work closely with Hoffman-LaRoche, the FDA and this Committee.

Thank you, Dr. Penneys.

DR. PENNEYS: Thank you, Dr. Jansen.

At this time, I would like to thank all of the presenters for their interesting information and declare the close of the open public hearing.

Thank you. The Committee will meet back here at 1:30.

[Whereupon, at 12:58 p.m., the Committee open session was concluded.]

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OPEN SESSION

May 8, 1989

Rockville, Maryland

We, the undersigned, do hereby certify that the foregoing pages, numbers 1 through 158, inclusive, are the true, accurate and complete transcript prepared from the reporting by Pamela Briggle in attendance at the above identified hearings, in accordance with the applicable provisions of the current GSA professional verbatim reporting and transcription contract, and have verified the accuracy of the transcript by (1) comparing the typewritten transcript against the reporting or recording accomplished at the hearings and (2) comparing final proofed typewritten transcript against the reporting or recording accomplished at the hearings.

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