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PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

JOINT MEETING OF THE

DERMATOLOGIC DRUGS AND THE

FERTILITY AND MATERNAL HEALTH DRUGS ADVISORY COMMITTEES

Monday, May 20, 1991

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C O N T E N T S

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P R O C E E D I N G S

DR. DAVIDSON: Good morning. We should begin today's deliberations in the interest of the time and the schedule. Since this is a combined meeting of two committees, it is probably appropriate that at least the membership of each of the committees identify and introduce themselves briefly.

I am standing in today for Dr. Hulka, who is the chairman of the Fertility and Maternal Health Drugs Advisory Committee. I am Ezra Davidson from Los Angeles, an obstetrician at the King-Drew Medical Center.

DR. MCKAY: I am Susan McKay from the University of Wyoming.

DR. BARBO: Dorothy Barbo, Maternal and Fetal, University of New Mexico.

DR. ROY: Subir Roy, gynecologist from the University of Southern California.

DR. FLEISS: Joseph Fleiss, biostatistician at Columbia University.

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DR. COSSMAN: Joanne Cossman, Dermatology Drugs Advisory Committee, consumer rep.

DR. MINUS: Harold Minus, dermatology, Howard University.

DR. LUMPKIN: I am Murray Lumpkin. I am the division director of the Division of Antiinfective Drugs Products, FDA.

DR. SCHROETER: Arnold Schroeter, Wright State University School of Medicine.

DR. ROUBEIN: Isaac Roubein. I am the executive secretary for this panel.

DR. DAVIDSON: Thank you. We would like to continue with the welcome.

WELCOME AND ANNOUNCEMENTS

DR. LUMPKIN: I would like to take the opportunity, on behalf of the Center, the Office, and the Division, to

express our welcome to all of you here today, members of the committees and the members of the general public. I would like to take this opportunity, also, to welcome a new member to the Dermatology Advisory Committee. That is Dr. Joseph McGuire from Stanford, who joins us today for his first meeting here. We have tried to get Joe on this committee many times in the past and we have finally been able to do so, and we are particularly glad to have him with us today.

DR. DAVIDSON: I think Dr. Roubein has some announcements.

DR. ROUBEIN: The following announcement is made a part of the record to address the issue of conflict of interest and the appearance thereof which bears on the submitted agenda for the meeting and all reported financial interests of this date.

It has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participating members and experts present no potential for an appearance of conflict of interest at this meeting. In the event that the discussion involves any products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to seclude themselves from such involvement and their seclusion will be noted for the record.

With respect to all other participants, we ask, in

the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. DAVIDSON: Thank you. The session is now open for the public hearing portion, beginning with a presentation by Roche, including the Slone study.

DR. ROUBEIN: Officially we have an open public hearing now for those in the audience. If anyone would like to make a comment, please come forward. Identify yourself and give your affiliation.

OPEN PUBLIC HEARING

DR. CRAWFORD: Thank you. My name is Dr. Stephanie Crawford. I am Director of Scientific Affairs for the American Society of Hospital Pharmacists. ASHP is based in Bethesda, Maryland. We have a membership of more than 23,000 pharmacists who practice in organized health care settings such as hospitals, managed-care settings, long-term care facilities, and home care organizations.

We appreciate this opportunity to provide brief comments to the combined advisory committees, the FDA, and this audience. We wish to comment on one of the agenda questions that will be posed to the combined committees this afternoon, that question being should the distribution of Accutane be restricted and, if so, how?

The priority of the pharmacy profession is to provide quality pharmaceutical care to patients. One aspect of that care is to ensure that drug products which have dangerous adverse effects are appropriately monitored and managed. In framing our position this morning, ASHP considered what, in our opinion, is in the best interest of patient care with respect to the distribution of Accutane.

Our current position is to support the current system of drug distribution in which prescribers and pharmacists exercise their professional responsibilities on behalf of patients. Clearly, Accutane is a drug product that is of tremendous benefit to the patient populations that it serves. Also, it is unquestionable that the drug product should not be used by pregnant women or by those who may become pregnant while on Accutane therapy.

We acknowledge that there may be limited circumstances in which the constraints on the traditional drug-distribution system may be appropriate if certain criteria are met. It is our belief that those criteria involve the following. First, the requirements are based upon scientific evidence fully disclosed and evaluated by physicians, pharmacists, and others. Of course, during this morning and this afternoon this is what these joint committees will do.

Secondly, there is scientific consensus that

requirements are necessary and represent the least restrictive means to achieve safe and effective care.

Third, the cost of the product and any associated products or services are identified for purposes of reimbursement, mechanisms are provided to compensate providers for special services, and duplicate costs are avoided.

Fourth, all requirements are stated in functional, objective terms so that any provider who meets the criteria may participate in the care of patients; in other words, the criteria for handling the drugs that require a higher level of monitoring should be clearly spelled out in order to allow those practitioners who are able to meet them to do so, and, finally, the requirements do not interfere with the professional practice of pharmacists, physicians, and others.

We do not believe the restricted drug distribution would be the best course of action with respect to Accutane. We have learned a lot from the initial closed distribution scheme of another drug product which many of you are familiar with, clozapine. That initial closed scheme, which involved only one provider and has since been scrapped, was, in our opinion, ill-conceived, questionably managed, prohibitively expensive, inaccessible, and unnecessary.

It is unknown if the question that is posed to these combined committees this afternoon involves drug distribution at the level of the prescriber or the dispenser, the

pharmacist. However, if there are contributing problems with respect to patient safety at the level of drug distribution, those problems must be identified. The professions will continue their efforts to address the problems and correct any apparent deficiencies.

We support the availability of the drug product and we would oppose any closed distribution system. If these committees do recommend, after looking at the scientific evidence, that there be an alternative drug-distribution system, we implore that you recommend to the FDA that they involve the professions of pharmacy, medicine, and others, the industry and the FDA staff, to develop any special criteria or procedures that may be necessary, acceptable, and effective to ensure optimal patient therapy.

Thank you for this opportunity to comment.

DR. DAVIDSON: Thank you. Any other public comments?

(No response)

We will now close the open public hearing.

Next on the agenda is a presentation by Roche, including the Slone study.

PRESENTATION BY ROCHE, INCLUDING THE SLONE STUDY

PRESENTATION BY ROBERT ARMSTRONG, M.D.

DR. ARMSTRONG: Good morning. I am Dr. Robert Armstrong, the director of Medical Affairs for Roche

Dermatologics. On behalf of Roche Dermatologics, I would like to thank the FDA and the advisory committees for this opportunity to discuss Accutane.

We have a great deal of information to present and review for you this morning, and in the interests of making our 11:05 goal for completion I would like to proceed with an overview of the presentation, for orientation purposes, so that the members of the panel and the group will have an idea about the information that is to come.

(Slide)

We will start with an overview of pertinent aspects of Accutane. That will be followed by a section discussing the pregnancy-prevention program. Since this is familiar to most members of the committees and the audience, there will be only a brief review of the originally implemented program and its key elements, with a concentration, instead, on the actions that have been taken since last year's meeting.

Following that discussion there will be a segment of the program on an evaluation of how the prevention program is working. We will then proceed with an analysis of the use of Accutane by women, in particular, with some comments on the epidemiology of acne, and then, finally, relate all of these parts to the questions the committee has been asked to address regarding labeling and distribution.

(Slide)

I would like to begin by making the point that severe recalcitrant cystic acne is, in fact, a serious disease. It typically has a prolonged course and it has proved to be unresponsive to oral antibiotics and other forms of therapy that were available before the introduction of Accutane.

Indeed, Accutane has proven to be the first extremely effective drug for severe recalcitrant acne and it is the only drug which will control most cases. Results are usually obtained in the four- to five-month recommended treatment period and remissions are usually prolonged, apparently indefinitely in many individuals.

(Slide)

This patient is an example of a pretreatment assessment, showing you the extent of disease that is possible with cystic acne.

(Slide)

This slide, taken just a few months later, at the conclusion of a course of Accutane, which shows the substantial improvement that this individual has experienced. I would point out, however, that there are residual scars left from the underlying disease and the scars are not expected to be eradicated by therapy. This is one of the rationales for treatment, in order to try to minimize life-long scarring.

(Slide)

This is another aspect of Accutane which is quite important, and it is the focus of our considerations this morning, and that has to do with the birth defects that occur with high probability in the event of fetal exposure to the drug. It is for this reason that we have gone to a number of different efforts over the years to try and minimize the possibility of fetal exposure resulting in birth defects.

I would like to ask my colleague, Dr. Wanju Dai, to come and review with you the reports that have been submitted to Roche over the years on this issue.

PRESENTATION OF WANJU DAI

DR. DAI: Good morning. I am going to present to you the cases of pregnancy exposures to Accutane. These cases were reported to us either through the spontaneous reporting system or were collected from various studies.

(Slide)

One of the studies, the Slone Epidemiology Unit Accutane Follow-Up Survey, will be presented to you later by Dr. Mitchell. The information presented on these slides are more up-to-date than that which is included in your packages.

(Slide)

As of April 30, 1991, we have received a total of 577 pregnancy exposure reports. This table is done by pregnancy outcome and the year of commencement of Accutane therapy. We have received a total of 91 congenital

malformation cases and these included nine detected from abortuses and four from stillborn babies, as well as 78 live births.

More than 50 percent of the cases occurred in the first two-and-a-quarter years of marketing, prior to 1985. The remainder, less than 50 percent, have occurred in the more-than-six-year period after 1985.

This one case, whose mother had commenced Accutane therapy in 1990, was an abortus. In addition, there were three birth defect cases that were born in 1990 whose mothers had commenced Accutane therapy in 1989.

We believe that the vast majority of the birth defect cases in association with Accutane were reported to us. There has been considerable publicity regarding Accutane and birth defects since 1988. However, this publicity did not increase the reporting of congenital malformation cases to us.

In addition, at the end of last year the Office of Epidemiology and Surveillance of the Food and Drug Administration had solicited previously unreported birth defect cases in association with Accutane therapy from 1600 specialists who were involved in infant care and they have not been able to confirm any previously unreported birth defect cases in the United States from this request.

Based on the PDS data base, it was estimated that approximately 57,000 women of childbearing age were exposed to

Accutane in 1990, and we have received a total of 50 pregnancy exposure reports where women had commenced Accutane therapy in 1990.

(Slide)

Similar to what I had done last year, I have examined the causes and the timing of pregnancy exposures to Accutane. There were a total of 55 pregnancy exposures where the maternal exposure to Accutane was after January 1, 1990. We could estimate the timing of pregnancy exposures to Accutane in 51 cases. Seventy-five percent of these cases were conceived during Accutane therapy and 25 percent conceived prior to the start of Accutane therapy.

(Slide)

Among the 13 patients who conceived prior to Accutane therapy, two patients had used Accutane capsules that remained from previous Accutane treatment to treat themselves without the supervision of a physician. Five patients had pregnancy tests done at base line, prior to Accutane therapy, and these included three serum pregnancy tests and two urine pregnancy tests. In addition, three of these five patients were also told to wait until the next menstrual period before starting Accutane therapy. However, the patients did not follow the instruction.

There were five patients who did not have a base-line pregnancy test done and four of these five patients were

practicing contraception when Accutane was prescribed. The methods used by the four patients included two tubal ligations, one oral contraceptive, and one patient used spermicide and condom.

The one patient of these five patients who did not practice contraception when Accutane was prescribed actually was given a prescription for oral contraceptives and the prescriber of Accutane had advised the patient to start the oral contraceptives one month prior to starting Accutane and to wait until her next menstrual period before starting Accutane. Apparently the patient did not follow the instruction.

(Slide)

There were 38 patients who conceived during Accutane therapy. The majority of them, 21 of them, did use contraceptive methods during Accutane therapy. The methods used by these 21 patients included seven using oral contraceptives, six using barrier methods, five using spermicides alone.

In addition, there was one patient who had a tubal ligation eight years ago and another patient whose sexual partner had a vasectomy. There were seven patients who claimed to be abstinent when Accutane was prescribed, and there were also four patients who were known to be sexually active when Accutane was prescribed, and they did not practice

contraception during Accutane therapy. Two of these four patients were actually given prescriptions for oral contraceptives by their prescribers, but the patients did not fill the prescriptions.

The other two patients of these four were detected in the Slone Accutane follow-up survey. One of these two patients had a previous history of induced abortion, and the patient did not practice contraception as advised by the prescriber. We have not received sufficient information on the other patient as yet. There was one patient who treated herself with Accutane capsules that were left from previous Accutane treatment.

It appears from the review of the most recent pregnancy exposure cases that physicians have been conscientious in advising patients to avoid pregnancy exposures during Accutane therapy. Based on the cases on which we have sufficient information, the physicians have at least verbally warned the patients of the pregnancy risks during Accutane therapy before prescribing Accutane.

The vast majority of the pregnancy exposures occurred during Accutane therapy and contraceptive failure, including both human failure as well as betha (phonetic) failure, was a major cause of these pregnancy exposures.

Thank you.

PRESENTATION OF ROBERT ARMSTRONG, M.D.

DR. ARMSTRONG: I would like to now review the reasons why Roche believes that the majority of birth defects have been reported to the company. We recognize that there may be unrecorded cases and that time may prove that additional ones are or will be presented, but our reasons for believing that most of the cases have been reported begin with the information generated by the Slone Epidemiologic Unit survey.

(Slide)

Through the end of last year nearly 57,000 women had chosen to enroll in this survey. The follow-up from the survey is 11 months, so it is clear that many of the patients who enrolled in 1990 have yet to complete their follow-up and it is possible that as we get additional information from the follow-up this may change, but as of now, as of today, no cases of birth defects have been identified through this survey.

(Slide)

Dr. Dai has already reviewed for you the information that FDA has sought, new case reports from neonatal experts, experts in neonatal health, and they have not identified a new confirmed case from the United States from this effort.

(Slide)

Also, in the past, a number of data bases have been

reviewed for the possibility of yielding information on birth defects and those data bases include Michigan Medicaid, the Group Health Cooperative of Puget Sound, and the Harvard Community Health Plan, and there is not an overwhelming number of cases that have been identified through these -- I believe there are actually two cases from Michigan Medicaid, and I will say more about that later. No cases from the other two data bases have been identified.

(Slide)

As Dr. Dai has also mentioned, we have had quite a bit of publicity about this concern over the past three years. Generally, with an increased amount of publicity there is a corresponding increase in the amount of spontaneous reports, and the number of spontaneous reports that have been received by the company is actually not an indication of any substantial or massive underreporting of birth defects.

Finally, we have gotten some cases of birth defects identified through various birth defect registries around the country, but actually the number is quite small and is included in the 91, total, cases summarized for you by Dr. Dai.

(Slide)

In 1981 the FDA's Office of Epidemiology and Biostatistics attempted to quantify the degree of underreporting by looking at the Michigan Medicaid data base

and also at experience from the Group Health Cooperative of Puget Sound. I would like to review now a contrast between the information which was available in 1988 and that which is available today.

(Slide)

In 1988, and then updated in 1990, a rate of 5.9 percent pregnancy exposure was presented by OEB based on suspected pregnancy exposures using OEB criteria. However, we had pointed out then and in the time since that the criteria were useful for identifying suspected cases, but that case verification was important to determine if maternal ingestion of Accutane had occurred at a time that would involve fetal exposure and if, in fact, that fetal exposure had resulted in birth defects.

In February of this year, at a meeting with the Accutane monitoring group here at the FDA, these data were presented to us, that is, that the number of malformations that had been identified through Michigan Medicaid was two. One of these cases had been previously reported to Roche through the spontaneous reporting mechanisms. The second case is a case that had not been recognized by the physicians caring for the patient as having been related to Accutane ingestion, and so was identified for the first time as a result of this effort.

Another eight cases from this case verification were

reported as being normal. One infant died as an obstetrical catastrophe, I understand, because of a cord around the neck. Linkage between the maternal and neonatal records had been unsuccessful in three cases and had not been attempted in an additional two.

(Slide)

Going now to the Group Health Cooperative from Puget Sound, again, in 1988, OEB estimated pregnancy exposure rates of 1.9 percent based on three suspected pregnancy exposures from this data base. This group has recently published its experience in a peer-reviewed journal, The Archives of Dermatology, and a review of that article, which has been submitted to the committee members, includes that one of these cases was actually an unexposed pregnancy, where Accutane was taken well after the one-month period of recommended contraception following treatment.

In two instances the patients proved to have amenorrhea but with a negative pregnancy test and, therefore, were not actual pregnancy exposures. There was in this report one instance of a noncompliant patient, so described because the patient had failed to return for follow-up visits as scheduled, who apparently elected to take leftover medications without medical supervision. Again, from this data base, no instances of birth defects were identified.

(Slide)

In 1988 Roche began to pull together a program to unify and reinforce the various messages that had been in effect from the time the drug was introduced and had been modified over the years in light of the experience.

(Slide)

This pregnancy prevention program is one that you have had presented at this committee in the past, so I plan to outline only the key elements.

(Slide)

I would begin by pointing out that strict prescribing criteria are now provided in the package insert labeling as guidelines for the selection of correct patients.

(Slide)

Those patients who are not on effective contraceptive regimens and who would profit from evaluation and counseling may now get that counseling, at Roche expense, by our referral program. Under this program patients may be referred to an appropriate health care provider for contraceptive counseling and an initial pregnancy test.

(Slide)

Also, for the first time for a prescription drug, labeling now includes a consent form, a copy of which is also provided with the materials to support the proper use of Accutane, and this consent form goes into great detail about

the important facts of how the patient needs to approach the use of Accutane to use it properly. Attached to this consent form is a follow-up enrollment form for the survey that Dr. Mitchell will be discussing later in this presentation.

(Slide)

Finally, in 1989 new packaging was introduced. This new packaging included significant warnings and patient information as an integral part of the capsules that were dispensed as a way of assuring that the information would get to all patients who received medication.

(Slide)

And, again, the follow-up survey that I have mentioned.

(Slide)

In order to effectively implement this program, Roche has cooperated with a number of different medical, pharmacy, and other societies to increase education about the proper use of the program.

(Slide)

What has happened since last year? I want to review very briefly the steps that have been taken since our meeting last year on the recommendations made by these committees.

(Slide)

First, we have implemented a program to reinforce the importance of base-line pregnancy testing and informing

patients of the importance of waiting until the second or third days of their next normal menstrual cycle.

These are two of the components of the campaign which we have launched, entitled "Start Right or Don't Start." (Slide)

Other components of this campaign are included now on the packaging, highlighted for patients' attention and separated from the other material. In addition to the first two steps, there is a note that the patient must use effective birth control one month before, during, and one month after taking Accutane, and also that the patient must sign up for the confidential follow-up survey.

(Slide)

One of the questions that has been discussed in the past is the difficulty in patients understanding this information, if English is not their primary language. In order to address that concern, we now have an 800 telephone number available in the 13 most commonly spoken languages in the United States. These materials are also soon to be available in written format for all of the materials that are available for patients to use on request by the prescribing physician.

(Slide)

In addition to these programs, Roche has also provided support for a continuing medical education videotape

regarding contraceptive practices jointly developed by the American Academy of Dermatology and the American College of Obstetricians and Gynecologists.

One of the proposals made for consideration last year had to do with making modifications of the prescription form as a means of incorporating some of the relevant information on the same form that Accutane was being prescribed on. We as a company had reservations about the utility of this approach, but undertook to convene a meeting of pharmacy and medical societies to discuss the practical applications of such a program. This meeting was held in October of last year and included five medical societies and six pharmacy organizations.

The nature of this meeting was not one to develop a position paper but, rather, that individuals selected by these societies could provide their opinions, and in no way do these represent formal position statements from the various societies that attended. It was, however, the consensus of those who attended that the prescription form was not a suitable place for patient information, that that was better included in the patient's confidential medical record, and, furthermore, that use of prescription forms would be easily circumvented under current pharmacy laws that provide for the prescribing of drugs by telephone, without requiring any written record.

We have, also, in response to suggestions made by the committees, prepared a videotape that physicians can use in patient education. This videotape is in the process of being tested with both physicians and consumers to find out how effectively the message is being conveyed, and we expect that this will be completed and made available to prescribing physicians some time in the near future.

(Slide)

Finally, I would like to take a moment to mention our returned goods program, which we expect to begin quite soon. We actually propose to do this as two pilot programs for returning unused capsules which remain after the completion of a course of treatment. In one program, dermatologists will be supplied 1000 kits of materials to give to patients to return unused capsules. The other program will ask pharmacists to supply 1000 patients with materials for returning unused capsules.

These two pilots are intended to be run in geographically distant places, so that there will not be overlap in the patients between the two, and at the conclusion of the handing out of these materials it will be possible to compare the number and rates of return under the two programs to find out what contribution they might make, and to make a decision about whether the program should be expanded or discontinued.

(Slide)

This is an ambitious program with goals to try and accomplish and one of the things that we thought was important was to try to look at ways to evaluate how effectively it was being implemented.

(Slide)

One of the efforts involves the ongoing monitoring of prescribing physicians, both dermatologists and nondermatologists, and as a result of this ongoing monitoring we continue to find that approximately one in five women who are evaluated with a pregnancy prevention kit do not get a prescription for Accutane. We see this as evidence that the kit is useful in identifying women who are not appropriate candidates and having them receive treatment with other modalities.

(Slide)

Another program that has been presented in this forum in the past as an assessment of the pregnancy prevention program's work is the Harvard Community Health Plan. I understand there is time later in the day for a more detailed presentation, but I did want to take this opportunity to make a couple of points about this before that presentation began.

First, in this assessment the pregnancy exposures were looked at in two periods, before and after April, 1988, finding a 2.5 percent pregnancy rate in both periods. We

would like to point out that the April, 1988 date is a very appropriate one for measuring the success of the pregnancy prevention program itself, because it was only in September of that year that the first elements of the program were actually introduced, that is, a full five months after April, and it was one year later before the availability of new packaging essentially completed all of the aspects of this program.

Nevertheless, within this experience it was clear that there were no birth defects that were identified through this program and it has also become clear in subsequent information which has been sent to the committees that all of these patients within this program had been informed of the risk either by signing informed consent or indicated that they had been told by their physicians of the importance of avoiding pregnancy.

Unfortunately, the information we have been provided on this program aggregated prescriber data over the entire treatment period, so it is really not possible for us to assess how those prescriber practices may have changed around the time of the intervention of these different parts of the program.

(Slide)

The most important means of assessing the success of the pregnancy prevention program is, however, the Slone Epidemiology Unit survey. I would like to ask Dr. Allen

Mitchell, Research Professor of Epidemiology at Boston University, to present his information on this study.

PRESENTATION BY ALLEN MITCHELL, M.D.

DR. MITCHELL: Thank you, Dr. Armstrong. It is a pleasure to be here this morning and to be able to provide some update of information that we have previously presented as well as some entirely new information.

(Slide)

The Accutane survey conducted by the Slone Epidemiology Unit was designed to assess compliance with the pregnancy prevention program among female users of Accutane. Specifically, its objectives were to determine the awareness of the teratogenic risks of Accutane, the history of prior acne therapy, the rate of pregnancy among women in the survey during Accutane therapy as well as in the month following therapy, pregnancy outcomes in this group, and risk factors for the occurrence of pregnancy.

In addition, we had intended as an objective to consider the impact of an intensive survey such as this on compliance itself. Needless to say, this is a complex undertaking. The SEU is entirely responsible for the design, conduct, analysis, and interpretation of the data, but this has been done in concert with an independent advisory committee, chaired by Dr. Paul Stolley.

(Slide)

This committee has been an extremely active and helpful committee, has met with us eight times over the period of this survey, and has provided extremely useful insights as well as criticisms, both constructive and -- well, constructive. I cannot remember any that were not.

(Laughter)

(Slide)

The survey has limitations. First of all, clearly, since it began in 1989, there are no equivalent base-line data against which to compare our findings.

Number two, given the urgency with which the survey had to be mounted, there was no opportunity for pilot studies. As we understand it, this survey is unique in many ways, and so we were, to a large extent, limited in not being able to pilot test a number of the components of the survey.

Number three, the survey is itself a form of intervention. Women who participate are contacted in one way or another, but let me stress that this is largely a nonissue, because the survey is to be included as part of the pregnancy prevention program for as long as that program is in existence. As we will discuss later, there are different levels of intervention, but in the postal follow-up component of the survey the intervention is quite minimal.

(Slide)

The fourth limitation is, of course, the one of

greatest concern. Survey participation, like the pregnancy prevention program itself, is voluntary, and, therefore, survey participants may not be representative of the entire population of women using Accutane. Indeed, there was no way, in advance, in the design of the survey to assure representativeness of that population.

(Slide)

Let me focus for a moment on the design of the survey.

(Slide)

First, let me draw your attention to the period of Accutane exposure, which was projected to be approximately five months, and then we identified a six-month follow-up period, this period being sufficient to identify the first two trimesters of any pregnancy that might occur.

Women could enroll in the survey by any of three current enrollment methods. The first method, which became operational with the onset of the survey in January, 1989, was physician enrollments. It was only in May of 1989 that the medication package became available. That package included an enrollment form which gave the woman an opportunity to enroll if she had not been provided that opportunity by her physician.

In addition, the enrollment form, like the physician enrollment form, was designed to look and behave very much

like a consumer rebate, so it would be familiar and comfortable to women, and the hope was that this enrollment method might preferentially attract women who may be less compliant but who are attracted by the $10.00 payment which was provided to all women who enrolled in the survey.

More recently, in August of 1990, we introduced a toll-free 800 number by which women could also enroll in the survey. We will not be providing much data from that for obvious reasons, it having been so recently introduced.

Once the enrollment is sent by the woman and received by us, within 48 hours she is sent a check for $10.00 and told that she will be followed by one of two methods: Five thousand women a year are randomized to be followed by telephone and remaining enrollees are randomized, obviously, to be followed by mail.

In the telephone follow-up there are two contacts during Accutane therapy. The first occurs within the first month of enrollment and the second occurs in the midst of Accutane therapy. This provides information, clearly, that is current during the period of treatment, at the beginning and in the middle. A final interview is conducted six months after the woman has completed her course of Accutane therapy.

In contrast, in the mail arm of the survey there is no contact with the woman other than the payment of the $10.00 until approximately one month after her anticipated course of

therapy is completed, and that is basically a tracing contact, and then six months after the course of Accutane is completed, equivalent to the telephone interview, a mail questionnaire is sent to the woman.

(Slide)

These two follow-up approaches have different strengths and different weaknesses, of course. In terms of the information they provide, the telephone approach allows us to determine pregnancy occurrence and rates, pregnancy outcome, and also enables us to consider compliance with the pregnancy prevention program both at the onset of therapy and in the midst of therapy.

The mail arm, in contrast, essentially provides us only the pregnancy information.

The advantages of the two are identified below. The telephone arm, because it is essentially prospective, is free of recall bias, a problem that could certainly occur in the mail arm.

In contrast, the mail arm is free of the interventions that are inherent in the telephone arm, and the mail arm provides only minimal intervention with the woman who is enrolled.

(Slide)

This is an outline of the presentation that follows now. We have presented much of the information on methods in

the handout materials last month and I will not go into that in great detail, and we will focus more on the survey objectives. In particular, we will examine the 1989 report, which represents a population with considerably large numbers, essentially two-thirds, of the women who have now completed their follow-up.

In that large population with completed follow-up we will consider patient and physician characteristics at the onset of treatment, in the midst of treatment, and in relation to the enrollment method. We will also consider pregnancy rates.

In the 1990 cohort, these women obviously being more recently enrolled and where follow-up is far less complete, we will really look at the population to determine whether there have been changes in patient or physician characteristics which are either worrisome or encouraging with respect to projecting future results.

We will focus some attention on the representativeness of the survey population and come to some conclusions.

(Slide)

First, let us consider enrollment, and what we are going to be doing is looking at the period, January 1, 1989, when physician enrollment forms became available, through March 31, 1991, representing the nine quarters of the survey.

(Slide)

This histogram presents the absolute number of enrollments according to survey quarter for the period that I described. As you can see, in the first three months of the survey there were no medication package enrollments -- the hatched bar refers to physician-generated enrollments, the solid bars refer to medication-package-generated enrollments, and this top bar refers to telephone-generated enrollments. As you can see, the early months of the survey were women enrolled exclusively through their physicians.

In May of 1989 the medication package became available and we began to see some medication package enrollments. But it is really only from July of 1989 onward that we begin to see the enrollment reflecting the large numbers of women who use the medication package, and from that point onward approximately 8000 to 10,000 women enrolled in the survey each quarter. In fact, in 1989, 83 percent of enrollments came in the last six months and, for all practical purposes, one could consider the survey to be done in July of 1989.

What is interesting in this histogram are two points, I think. First of all, what we see in the two most recent quarters are absolute increases in the number -- small, 5 to 8 percent -- but absolute increases in the number of enrollments relative to the equivalent quarter the previous

year.

Secondly, what we see is what appears to be an increasing proportion as well as absolute numbers of physician-generated enrollments in these last two quarters. We will talk more about that as we move on.

Based on this first quarter's experience and the relative distributions in previous years, we would project 38,000 women, roughly, to be enrolling in 1991.

(Slide)

As I mentioned, when we look at the distributions of the telephone and mail follow-up -- this information was largely presented in the handout -- in 1989 there were over 21,000 women who enrolled in the survey. Approximately 6000 of those were randomized to the telephone arm. In 1990 over 35,000 women enrolled in the survey and approximately 5500 of those were randomized to the telephone arm.

In terms of our follow-up success rate for women who were eligible for follow-up, recall that we have indicated in the past that start-up was quite slow. The survey began in January, 1989, As enrollments came in, women in the telephone arm immediately became eligible for their first, and soon their second, telephone interviews. Since we did not have adequate well-trained staff to complete all those interviews, approximately half of the telephone sample had to be transferred into the mail sample for follow-up. That was

essentially a random phenomenon. The overall follow-up rate for the telephone group, whether by telephone or by mail, for 1989 of the eligibles is 88 percent, and similarly high follow-up rates have occurred for women assigned to the mail arm, where it is approximately 90 percent both for 1989 and 1990.

In the 1990 cohort of women in the survey, the telephone follow-up is approximately 97 percent now that we have adequate staffing.

(Slide)

What are our conclusions in terms of the method? Quite simply, the survey seems to work from a procedural standpoint. We are enrolling 35,000 to 40,000 women per year based on 1990 data and projected 1991 data. While the enrollment rate, in absolute terms, is unknown, it would appear to be stable or even increasing, given estimates of Accutane use among women, which you will hear more about as the day wears on, and follow-up has been successful among women enrolled in the survey.

(Slide)

I would like to turn our attention now to the survey objectives themselves and consider the 1989 cohort. As Dr. Armstrong mentioned, on average, if a woman has a five-month course of Accutane, she first becomes eligible for follow-up at 11 months and that follow-up, obviously, can take a few

months. So it is really the 1989 cohort (and most of those women, 83 percent, enrolled in the last six months of 1989) that provides us the opportunity to look at a completed sample.

(Slide)

What I would like to do first is look at the patient and physician characteristics as identified in the first and second telephone interviews that are conducted at the beginning and in the midst of therapy.

(Slide)

The mean age and education of this sample in 1989 was 27 years for age and 14 years of education, or two years of college.

(Slide)

In 1989 we asked only limited questions on the severity of acne. This table presents the number of years of acne among interviewed women. As you can see from the distributions, the large proportion of women had had acne for quite a number of years. Similarly, we asked additional questions about the previous courses of Accutane and the proportion of women who had had visits to their physicians for acne prior to the prescription of Accutane, the latter figure being 96 percent.

(Slide)

In terms of responses to the questions asked at the

first interview, "Did your doctor discuss the importance of any of the following before prescribing Accutane," what we found is a variation in the proportion of affirmative responses. For example, they ranged from a high of using effective contraception as an instruction in 84 percent of the women to postponing Accutane until the next menstrual period, which in 1989 was reported by 64 percent of the women. So there was a variation in the apparent compliance by physicians with the instructions provided in the pregnancy prevention program.

(Slide)

Of more interest was the number of women who reported having a pregnancy test before starting Accutane -- in 1989, again. Forty-eight percent reported having had a serum pregnancy test, 6 percent reported having had a urine pregnancy test, 8 percent reported a pregnancy test of unknown type, for a total of 62 percent reporting having had a pregnancy test, where 34 percent indicated that they did not, to their knowledge, have a pregnancy test. These figures were clearly lower than we would have expected relative to other physician behaviors that were identified, and we will talk about that a little more later.

(Slide)

In order to identify pregnancy rates, it as important to identify pregnancy risk categories, and we

created categories of hysterectomy, infertility, not sexually active, two groups of sexually active women, those using birth control and those not using birth control, and unknown. As you can see, the largest categories were the nonsexually active, which included 35 percent of the survey participants. Sixty-two percent of the participants reported being sexually active. Ninety-nine percent of those reported using birth control.

The 1 percent in this sample, 30 women, who reported being sexually active but not using birth control were originally identified as program failures in our protocol. We have changed that name because we have clarified that definition. We now call them high-risk behaviors and, for reasons that are overwhelmingly ethical, in approaching them we felt it was critical, if our interviewer was confronted by that situation, that the women be read a warning and that other interventions take place. So this very small subgroup in the telephone arm is indeed exposed to interventions that would likely reduce their risk of pregnancy.

However, the large groups are the two groups, 35 percent, who were not sexually active, and the 61 percent of the sample who were sexually active and using birth control.

(Slide)

The distribution of contraceptive method in this population among contraceptors: First of all, we have broken

it down into five age categories. The two extreme categories are age under 15 and age over 44. Bear in mind there are only five young women in this group, the youngest group, and only 53 in the oldest group.

What you see in terms of contraceptive method is that, as one would expect, birth control pills are the choice of contraception among younger women and decline with age, running about 80 percent in the youngest women down to 4 percent in the older women, whereas various methods of sterilization, vasectomy and tubal ligation, hysterectomy, become the methods of choice and the more prevalent methods among women in the older age categories.

(Slide)

Let me focus for a moment now on information derived from women in the telephone arm in the midst of Accutane therapy. This was done, of course, to determine whether their compliance persisted into the midst of therapy. In response to the open-ended question of "what was the most important instruction given to you by your doctor," 86 percent of women volunteered that avoiding pregnancy was the most important instruction.

In terms of sexual activity at the first interview versus the second, 6 percent of the women who were sexually active at T1 were no longer sexually active at T2. In contrast, 19 percent of women who were not sexually active at

T1 become sexually active at T2. Contraception in these two groups was quite high. Among the women who stayed sexually active, 100 percent identified that they were contracepting. Among the 19 percent of women who had become sexually active between T1 and T2, 99 percent of the women in the 1989 cohort had also become contraceptors.

(Slide)

I would like to briefly compare the physician-generated and medication-package-generated enrollment methods, because they offer some insights into the characteristics of the populations. First, let us look at the characteristics of the physicians and the physician behaviors.

The larger proportion of women enrolled through the physician-generated method, 98 percent, had dermatologists as their prescribing physician, whereas in the medication-package-generated group 90 percent of the women reported dermatologists as their prescribers.

(Slide)

For the various physician instructions -- and it is not even important to identify the specific instructions -- for each of the instructions women who were enrolled by their physicians consistently reported higher rates of that instruction than women who had enrolled by themselves through the medication package. The same pattern obtained for pregnancy testing.

(Slide)

When we now consider the two methods with respect to the characteristics of enrolled women themselves, we find that the women enrolled through their physicians are slightly younger, one year younger, 26 versus 27 years of age, but the educational levels and duration of acne were virtually identical in the two groups.

(Slide)

Let us examine the 1989 cohort with respect to pregnancy information based on completed follow-up at the T-final and M-final questionnaires.

(Slide)

The first question I think needs to be addressed is are women in the two follow-up approaches comparable? I think this slide demonstrates that indeed they are, based on the first telephone interview versus the final mail questionnaire. What we found are remarkably comparable rates of reporting of physician instruction.

For example, "Did your doctor discuss possible side effects?" Ninety-seven percent versus 98 percent. Using contraception, 62 percent versus 59 percent. So it would appear that the women are indeed comparable in the two follow-up groups and, in fact, we find the same kind of comparability when we examine the duration of completed Accutane treatment.

(Slide)

We have added this third group here. We have a telephone group, which is women who were followed exclusively by telephone, a mail group of women followed by mail who had originally been assigned to mail, and a mixed group, which is essentially women who had been transferred from the telephone to the mail arm because their eligibility for the telephone interview had expired in the early months of 1989.

What we find is that the median duration of Accutane therapy is 140, 142, and 141 days. This is for the 99 percent of the survey population who reported use of the drug for less than a year, 364 days or less.

(Slide)

Now let us examine the pregnancy rates that we have observed, first looking at the risk period of the Accutane course only, and this is expressed as the pregnancy rate per 1000 courses, each of which is 140 days.

In the telephone arm there were five pregnancies reported among 2400-odd women, representing 906 person years of Accutane exposure, a 2.1 rate per 1000, 140-day courses. In the mail arm there were 43 pregnancies, translating to a rate of 4.2, and in the mixed arm, seven pregnancies, translating to a rate of 3.6/1000. Remember, these data are confined to the 99 percent of women who used the drug for less than a year.

What we found here did not surprise us, that women

in the telephone arm would have lower rates of pregnancy than women in the mail arm (these are not significant at this point); at least in absolute rates they appear to be lower. This difference is not surprising and I think all of us had predicted, given the higher levels of intervention, and so forth, that women in the telephone arm would have lower rates of pregnancy.

What we found that was surprising, to us, at least, was that women who had enrolled through their physicians were not less likely to become pregnant; if anything, the data (again, not significant, by any means, at this point) suggest that perhaps women enrolled through their physicians were more likely to get pregnant than women enrolled through the medication package. That is compatible with some later information you will see.

(Slide)

When we examined the risk period in the 30 days following Accutane treatment, again using the same three categories and now expressing it as rate per thousand enrolles, each enrollee contributing a month, essentially, the numbers are relatively small in the telephone arm and in the mixed arm. The rates are generally compatible, around 1.2/1000 enrollees.

(Slide)

We examined the pregnancy rate among that 1 percent

of women who had been on Accutane for one to two years. This is based on preliminary information; we have not confirmed these pregnancies. Obviously, as the duration extends, so does the follow-up come up later, but what we have observed -- expressed now as a rate per 100 person years -- is a considerably higher rate of pregnancy, perhaps 10- to 20-fold higher, if these numbers hold up, than is observed among short courses of Accutane therapy. It is a small sample of women and it is a small number of pregnancies that have not been confirmed, but it bears watching.

(Slide)

What do we know from the 1989 cohort in terms of total number of pregnancies? A total of 77 pregnancies has been identified to date. In 12 percent of the pregnancies the women were pregnant at the start of Accutane treatment (this is lower than some other estimates which have been provided). Sixty-six percent became pregnant during treatment and 22 percent became pregnant within 30 days of stopping their medication.

In terms of serum pregnancy testing, or any pregnancy testing, in this group which was pregnant at the start of Accutane, the proportions are quite comparable to those provided by Dr. Dai in her summary, and I will not elaborate here.

(Slide)

Among the 51 women who became pregnant during Accutane treatment, 14 reported no method of contraception; one vasectomy; seven using the pill (remembering that the pill was a very common birth-control method in the population); IUD, one; diaphragm, six; condom, 11; rhythm, three; "other," four; and unknown, four.

This is also compatible with Dr. Dai's information.

(Slide)

The primary contraceptive method among the 17 women who became pregnant within 30 days of Accutane treatment is roughly comparable: Six of the 17 reported no method, five on the pill, two with diaphragm, two condom, and one rhythm method, and one "other."

(Slide)

We also examined the outcome of pregnancy among the 60 women with pregnancies who were exposed during Accutane treatment -- remember, 60 exposed during, 17 exposed in the month following. Seventy-seven percent of the women reported having had a therapeutic abortion, 15 percent a spontaneous abortion, one woman, or 2 percent, having an ectopic pregnancy. There were two live births, for 3 percent, and among the two live births, one was reported as normal by the mother, but she refused follow-up by our consulting teratologist, Dr. Ed Lammer. One was reported by the mother as normal and Dr. Lammer is making arrangements to visit and

examine that infant.

(Slide)

In terms of the 17 women who became pregnant within 30 days of stopping Accutane treatment, the therapeutic abortion rate was 47 percent, 12 percent spontaneous abortions, 6 percent ectopic pregnancies, and there were 35 percent of these resulting in live births. One of them has been examined, with a normal outcome, five are pending follow-up. No malformations have been reported by the mothers to us, but, as I indicated, we have not had the opportunity to follow up and examine the five infants by Dr. Lammer.

(Slide)

We also took the opportunity to look at the pregnancy rate in the six months following Accutane use and combining the mail and mixed follow-up arms provides us with almost 12,000 women. Remember that follow-up occurs at six months after discontinuing Accutane therapy and so it gives us an opportunity to look at pregnancy rates in the following six months. This month, of course, is the 30 days following Accutane therapy.

What we found in terms of rate per thousand person months is an increase in the rate of pregnancy after women are off Accutane and after they have been off Accutane for 30 days. This is a very different experience from women's pregnancy occurrence while on Accutane. Overall it is an

approximately four-times-higher pregnancy rate for this five-month period compared to the five-month course of Accutane therapy in the same population.

Also of note is that in this population 28 percent of the women reported having had therapeutic abortions, a rate comparable to the general population. That is, I think, of some interest.

(Slide)

Now let us focus on the survey objectives from the 1990 cohort, and here the question we are trying to ask and answer is, is the population in 1990 different from 1989? Very briefly, we can say that the age distribution and education distribution are virtually identical in the two years of the survey. In terms of acne severity, we introduced new and more specific questions in our ongoing attempts to clarify the question. We introduced those questions in December of 1989.

In terms of duration of acne, which question was asked in both cohorts, 1989 and 1990, there were no differences in the distributions of duration, but we did ask some additional questions, and I will briefly present some of those results.

These are self-reports of cysts at any one time, according to the presence of scarring. As you can see, 60 percent of the women reported having had scars. Six hundred

forty-five of the women, a little over 10 percent, reported having had six or more cysts and scars, and 23 percent of the women reported having neither cysts nor scars.

(Slide)

We asked additional questions. For example, "When you started Accutane, how much did your acne bother or worry you?" (I apologize that this is not reported according to enrollment method.) Among the 4900-odd women, 91 percent of the women reported that their acne bothered them moderately or quite a lot.

(Slide)

When we looked at past treatments for acne, we found that the large majority of women, 95 percent, reported having been treated with antibiotics prior to their receipt of Accutane, 78 percent reported having been treated with Retin-A.

Self-reports of acne severity are very difficult for us to interpret; they seem to be difficult for the scientific community at large to interpret. Based on the recent AAD consensus conference on acne classification, and based on detailed and lengthy discussions with our own advisory committee, we have concluded that self-reports are really inadequate to assess acne severity.

(Slide)

Another matter of concern was what appeared to be a

low rate of pregnancy testing, and so we examined the 1990 (and, in fact, even the 1991 data) to determine whether the prevalence of use of pregnancy testing was increasing over time. What we found was, indeed, in the last months -- in the first six months, remember, we had women largely enrolled by their physicians, where pregnancy testing was fairly prevalent -- but from July of 1989 onward what we found was that somewhere around 55 to 57 percent of women reported any pregnancy test and only 42 to 45 percent reported having had a serum pregnancy test.

In contrast, in the last quarter of 1990 and in the first quarter of 1991, we see what appears to be an increasing prevalence, from 55 and 57 to 63 and 66 for any pregnancy testing, and in the serum category we see increases from 43 and 45 to 48 and 53. It suggests that physicians are obtaining pregnancy testing in a larger proportion of women, and this would logically result from a number of efforts.

We would like to think that part of it is the result of a newsletter that we sent out to all potential Accutane prescribers in the fall of 1990 which provided some feedback on the survey and also stressed the importance of enrolling all women and performing pregnancy testing, which was an issue identified by the survey.

Probably more likely what explains this are the activities that were undertaken by Roche at the same time.

They largely fall into two categories: repeated educational efforts directed at prescribers to assure that pregnancy testing is obtained; and the introduction of a new blister pack with the four prominent "you must" warnings (that was in the fall of 1989 and we would imagine that that has had some effect on what appears to be an increasing rate). For 1990, also, the risk categories appeared to be the same.

The distributions appear to be virtually identical to those observed in 1989. Contraceptive use and contraceptive methods, similarly, were quite comparable in the 1989 and 1990 cohorts.

(Slide)

Having reviewed the completed follow-up of women in 1989 and having observed no major differences in the 1990 enrollees, we now turn to the question of representativeness. This can be broken into two parts. The first question: Are women in the survey representative of all U.S. women -- and, we believe, the key question here -- with respect to contraceptive use and contraceptive success?

(Slide)

In terms of contraceptive use, we looked at the distribution of contraceptive methods among nonsurgical contraceptors, comparing the 1988 National Survey of Family Growth, NSFG, which was conducted by the National Center for Health Statistics, with data from the 1989 cohort in the SEU

survey -- these are expressed as percents -- using the age categories provided in the National Survey of Family Growth.

What I think becomes apparent very quickly is that among the methods listed, the most effective being the pill, what we see is that women in the survey, consistently, in every age category, more commonly use the pill than do women in the general U.S. population. So the survey women are not the same as U.S. women with respect to their choice of contraceptive method.

(Slide)

The next question is what about contraceptive failures? This is a complicated slide and I would be happy to provide copies of this to the committee and others, but what we have tried to do is, based on Dr. Trossell's estimates of contraceptive failure, the lowest expected rates of contraceptive failure -- and this paper is almost universally acknowledged as sort of the gospel -- get a reasonable rate to use in projecting these data, given the high level of education, the high levels of motivation of this population, and the short course of prevention that is intended by the pregnancy prevention program.

These estimates I have to introduce as being both complex and crude and only approximate, but if you consider the observed versus the expected, given that we have approximately 67 percent of the 1989 cohort followed up, one

would have expected 42 pregnancies due to contraceptive failure, based on these methods, and, in fact, we observe 44. This, again, though crude, suggests to us that the rate of contraceptive failure among contraceptors that was observed in the survey is compatible with the lowest expected rates for their respective contraceptive methods.

(Slide)

We also have to consider the representativeness of the survey population in another sense: Are women in the survey representative of all female Accutane users? This can be examined by Accutane distribution by region from health plan data and from a consumer survey, which I will be discussing. What we found is that the proportion of women enrolling in the survey is directly compatible with the Accutane distribution by geographic region in the United States as provided to us by Roche.

Our efforts to match data with health plans, Health Data Resources in Rhode Island, proved to be impossible -- the company went out of business (having nothing to do with us, I hope). We have also been working with HID, which has a large number of data bases, and we found that we were generally naive to think that matching would be as easy as we had hoped it would be. That has proved to be difficult. We have had a wide range of rates of matching and they seem to be plan-specific, which makes us wonder about their validity. We have

not yet received from HID the age distributions among the enrolled and non-enrolled women. We will continue to pursue that.

To try to get some kind of information that would be more reliable, we asked Roche, because they had access to these contractors, to conduct a consumer survey -- or, actually, to expand the consumer survey that they had done in the past -- and I would like to spend a few minutes describing this.

(Slide)

This was only completed in April of this year, so these are brand-new data and we did not have the opportunity to provide them to you in our handouts. The objective was to identify the proportion of Accutane users who enroll in the SEU survey, a question that has plagued us from day one, and, number two, to characterize the enrolled and non-enrolled women. We identified a target of 400 female Accutane users.

(Slide)

The sample was drawn from the PDS alpha data base of dispensed prescriptions, having a household telephone number -- whether that number was accurate or not was not guaranteed in advance, of course -- and the sample was to be women who had received a new Accutane prescription between August of 1990 and February of 1991. The sample is nationally distributed, and we can talk more about how these 400 women

were actually located.

Suffice it to say at this point that there were almost 2000 women where calls were attempted in order to produce this sample of 400. We think, in our own review of the potential selection biases in this process, that they are minimal, although there may be a slight bias toward older women. Younger women may have been preferentially or selectively excluded by the way the survey was conducted, but not enough, we believe, to alter some of the findings.

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We first compared the consumer and SEU survey populations, 400 women in the consumer survey, and using the 1990 data, which were the most comparable in time, from the survey. As I have indicated, the age of the women in the survey was somewhat older, 30 years versus 27 years. Education was the same. The proportion whose drug was prescribed by the dermatologist was quite comparable. Interestingly enough, the enrollment method in which we compared our own equivalent times for our enrollment method, doctor, package, and telephone enrollment methods, were quite comparable in the two group.

In addition, the proportion reporting to be sexually active was 61 percent in the consumer survey, 63 percent in the SEU survey, and among that subset 94 percent in the consumer survey reported using contraception, and 99 percent

reported being contraceptors in the SEU survey.

(Slide)

The proportion of Accutane users who enrolled in the SEU survey based on the not-trivial number of 400 was 60 percent; 239 women indicated they had enrolled in the survey, 60 percent (that is for 1990).

(Slide)

We examined the characteristics of the enrolled and non-enrolled Accutane users as identified by the survey, and what we found is that the mean age of women in the consumer survey, those who enrolled in the Accutane survey were slightly younger than those who chose not to enroll. Again, the education was equivalent, the portion prescribed by dermatologists was similar.

Those who were sexually active, 64 percent of those who enrolled in the survey were sexually active versus 54 percent, so almost two-thirds versus a little more than half among the non-enrolled. This is not significant statistically; the sample is not that large. But there is a suggestion here that women who are enrolling in the survey are selected towards those who are sexually active as well as those who are somewhat younger.

(Slide)

The question is, are younger women being preferentially enrolled? The response to the question the

women were asked, "Did your doctor offer you the opportunity to participate in this survey," what we found is that among women under 40 -- well, actually, in women under 30 -- the proportion was roughly half who reported that, "Yes, my doctor gave me the opportunity."

But as we get into the two older age groups, 31 to 40, only 41 percent reported their doctors encouraging them, and in the women who were 41 and over, only 20 percent reported that their doctors encouraged them to enroll in the survey. Again, this is suggesting that doctors are encouraging younger women to enroll in the survey rather than older women.

(Slide)

Why did women not enroll, at least the reasons that they gave? Two-thirds indicated that they were too busy or not interested. Another 4 percent each reported -- and these are not mutually exclusive -- that they had stopped the medication, they were surgically infertile, they did not meet the criteria, they were not of childbearing age, and 21 percent a whole variety of other reasons.

In reviewing these reasons we found very little to suggest to us that the reasons for not enrolling had to do with being at high risk of pregnancy, and, in fact, looking at these numbers, there is, again, a suggestion that women choose not to enroll in the survey because they are at low risk or at

no risk for becoming pregnant.

(Slide)

Similarly, when we look at the choice of contraceptive method among contraceptors according to whether they enrolled in the survey or did not enroll in the survey, what we find is that 40 percent of the enrollees were on the pill. Sixteen percent of the women who chose not to enroll were on the pill.

In contrast, when you add up the categories of tubal ligation, vasectomy, hysterectomy, or sterilization, we find that among the enrolled women 44 percent were surgically infertile, presumably. Among the non-enrolled women 65 percent were surgically infertile, again suggesting that perhaps women who enrolled in the survey were more at risk for becoming pregnant than women who chose not to enroll.

Well, with slightly over two years of experience, there is clearly more that needs to be done. This is a unique undertaking. To suggest that we have not made mistakes would be to suggest that we are perfect, and I would hesitate to make that suggestion. But there is a lot of work.

(Slide)

First of all, we need to maintain and expand enrollments in any way we can. We need to follow-up the current enrollees, both in terms of pursuing the relatively small proportion of nonrespondents -- that is an ongoing

effort. We also have to complete and continue follow-up of exposed pregnancies.

We have to consider potential other initiatives, and these have not even been discussed with our advisory committee at this point, so they are just remote possibilities, but if, for example, we found that women in the telephone arm were indeed at much lower risk for pregnancy than women in the mail follow-up arm, we might want to consider some kind of mid-level intervention that involved educating women, as the package insert does, for example, at periodic times during their therapy.

We also need to modify our questionnaire to obtain more detail on contraceptive methods; in particular, we have to get information on duration of contraceptive use prior to Accutane. We hope to work with some experts in the field of contraceptive failure to embellish our questionnaire and make it much more effective at identifying true rates of contraceptive failure. We want to explore those issues of motivation and failure rates with respect to contraception.

Finally, we are going to continue our attempts to assess representativeness. We are going to struggle with the HID data base. We hope to repeat and expand the consumer survey, asking some more pointed questions and questions which will provide us more detail, and also, as we indicated, we are working right now with United Health Care, which is another

data base and a very large data base, but it offers the opportunity of providing more information upon which matching might be attempted -- that has been our frustration in the past. That is in the preliminary stages of discussion and we only can hope that we will be able to work something out.

(Slide)

So what do we conclude at this point in the survey? The results of the survey to date reveal high levels of understanding of the need to avoid pregnancy. They also reveal that physicians' instructions and compliance are variable. They are relatively high for such things as urging women to use contraception. They are relatively low for pregnancy testing, although there is a suggestion that the prevalence of pregnancy testing is increasing, at least over time, and presumably in response to some efforts.

Use of contraception is high in this population and its distributions are skewed toward the most effective methods. Pregnancy rates are low in this population and they are compatible with the lowest expected contraceptive failure rates.

As to the last point, we have certainly made some progress in the last year, and it has been encouraging, in trying to assess the representativeness. But I think the only comment we can make at the present time is that we cannot presently determine with confidence if women enrolled in the

survey are representative of all Accutane users.

I will be happy to answer questions at a later point in the presentation and thank you for your attention.

PRESENTATION BY ROBERT ARMSTRONG, M.D.

DR. ARMSTRONG: Now I would like to discuss a bit about the use of Accutane by women.

(Slide)

At the time we began this exercise, we were looking for ways of estimating use by women, and there were a number of criteria that we used to shift through the various available data sources. I can begin by the conclusion that our selection of the PDS data-base system was that it was the only system that met these criteria that we could identify. Indeed, as of today, we do not think that there is an alternative that provides all of this information.

We wanted data that would be projectable to give national estimates. We wanted data that would identify patients who had had no prescription activity in the preceding 12 months to give us a number that would be comparable to the incidence of use, as estimated, and we will discuss that later. We also wanted a system that would capture all prescription activity, regardless of the prescriber or pharmacy, recognizing that patients sometimes change doctors and sometimes change pharmacies in the middle of a course.

We also wanted a data set that would give

information about the patient's gender, and PDS does that for almost all patients, and patient age, and, again, PDS provides age data in over 95 percent of their respondents. We also wanted data that were derived with a consistent methodology from the time Accutane was first introduced in 1982 through the present, so that we would have a means of evaluating trends without having to address questions about changes in methodology and what influence that might have.

(Slide)

With that introduction, this slide presents the estimates of use from 1983, the first year that Accutane was available, up through 1990, the last year for which data are available. What I would put out very briefly here is that the use in 1990 is approximately half what it was in 1983, and I would point out that our efforts to influence the appropriate use of this drug did not begin in 1988, and so this actually represents the effect of a continuum of efforts over the period of time since 1983.

(Slide)

I would like to take just a moment to suggest projections from two data bases that have done work for FDA. One is the Harvard Community Health Plan and the second is the Group Health Cooperative of Puget Sound. Both of these are health maintenance organizations which are known and recognized as providing high-quality care, and in their

context we believe it is fair to say that they do not provide an incentive for overutilization of drug and, as is generally true, dermatologists are primarily responsible for prescribing this drug.

(Slide)

If we take the use in these two data bases and project it to the United States population, what we find is that from the Puget Sound group, from 1988, the nationwide usage would be about 41,000 women and, similarly, from the Harvard Community Health Plan, after 1988, about 40,000 women. Again, these numbers have clearly substantial confidence limits and those confidence limits would overlap the confidence limits of the PDS estimates, so we cannot make any comments about whether these are statistically significant differences.

(Slide)

A great deal of attention has been spent in the past three years related to how many women are appropriate candidates for treatment with Accutane. In 1988 the Office of Epidemiology and Statistics went to the National Health and Nutrition Examination Survey to find data about how many women would have severe recalcitrant cystic acne and came up with a number of 4000. Clearly, this was quite a lot lower than the 65,000 women who were estimated to be using Accutane at that time, and that discrepancy led to the contention that Accutane

was being prescribed inappropriately in 95 percent of women.

The 4000 number estimate was one that was generally recognized by practicing clinicians as not corresponding to their experience in practice and led them to suggest that the estimates were incorrect.

In the fall of last year we found that the primary data set for NHANES was available, and we have asked Dr. Robert Stern from the Harvard Medical School to obtain the primary data and look at them to see if we could find an explanation for this discrepancy. I would now like to ask Dr. Stern to come and present the review of his findings.

PRESENTATION BY ROBERT STERN, M.D.

DR. STERN: Thank you very much. I would like to spend these few moments talking a bit about the epidemiology of acne.

(Slide)

As I think all of us in this room, irrespective of specialty, know, acne is quite a common disease. In fact, in 1980 a federal survey, the National Ambulatory Medical Care Survey, documented that there were 10 million visits to physicians for treatment of acne. Fifty-eight percent of these were by women and 62 percent of these women were ages 15 to 24, and about 80 percent of these visits were to dermatologists. In fact, in 1980 there were about 1000 visits by women to each dermatologist practicing in the United

States, clearly indicating that at least as a whole acne is an extremely common disease.

(Slide)

Given this commonness, is severe acne rare? These estimates of only 4000 cases appropriate for Accutane would mean less than one woman out of these 1000 visits who would be an appropriate candidate, according to these earlier estimates from FDA.

(Slide)

Let us look a little bit to where these estimates came from and what might have been some of the errors that led to these estimates of very few appropriate women with severe acne. First of all, the FDA used NHANES published estimates of severe acne, and these were not the correct ones, as I will demonstrate.

Secondly, they used estimates of duration of cystic acne that are not supported in the limited medical literature on this topic.

Third, they used estimates of efficacy and tolerance of other therapies for the treatment of severe acne, again not supported by the medical literature.

I think most important in looking at all the statistical data we will be seeing today is that the decision whether to prescribe this drug, from a practitioner's point of view, is really based on risk and benefit and, in my opinion,

as both a dermatologist and an epidemiologist, these data can only give us very broad ranges for what might be appropriate usage levels.

(Slide)

Let us look at the NHANES dermatology examination study. It was a point-prevalence study started more than 20 years ago and conducted from 1971 to 1974. It was based on a nationwide probability sample of the U.S. population. This was a treated population. In fact, a substantial proportion of those who had acne were under treatment for acne, so, therefore, this tends to underestimate both prevalence and the severity in an untreated population.

In 1971 essentially all drugs currently used for the treatment of severe acne, with the exception of Accutane, were in wide use and approved for use. Except for Accutane, there have been no innovations in the treatment of acne from 1971 to the present time.

(Slide)

Let us look at who provided these examinations. More than 20,000 individuals were examined. One hundred five dermatology residents, working from a few days to a few weeks, examined these 20,000 individuals. Each dermatology resident saw an average of 197 patients, with a wide range from four patients to 638 patients.

(Slide)

The form had three parts. The first section was dermatologic diagnosis. The second section was a comprehensive dermatologic examination that took up more than 75 percent of the exam form. The third section was a section for complaints and treatment.

(Slide)

This illustrates the somewhat overwhelming -- more than 560 items -- form that each of the residents was asked to code. The diagnosis section is only these first five items. The physical exam all through here, and then complaints and treatment on this final page.

(Slide)

Not only were those more than 200 residents working from a few days to a few weeks confronted with more than 560 items to code, this is the diagnostic lexicon they were provided: 91 groupings of diagnoses and over 500 diagnostic terms, something that most of us would take more than a few days to master. In fact, there were three separate diagnostic codes for acne, which were acne vulgaris, cystic acne, and acne not otherwise specified (I have not been able to figure out what that one was).

(Slide)

This is the section of the physical examination form which, I submit, provides our best estimates of what, in fact, these residents saw. As you can see, it asks whether acne was

inactive or active, asks to give degree of acne, and then asks about the presence of cysts, of two types of scarring, and locations of acne.

One can also see, as I will show in a moment, that, in fact, there are not "yes/no" questions, and some responses, such as the diagnosis of severe acne, implied other responses, which were often not completed by the examiners.

(Slide)

For example, if you were at the diagnosis of severe acne, this represents one end of the spectrum of severe cystic acne, acne conglobata, where both the face and the neck are severely involved, with extensive lesions, with scarring and cysts. Yet if one looks at everyone coded as severe acne, there was a substantial proportion of both males and females who did not have cysts and scarring coded; not that they were coded as being absent but, rather, people coded severe and said let us go on to the next of these 562 items.

(Slide)

But, in fact, the OMB estimates of severe cystic acne did not come from the dermatologic physical examination, the disease-oriented examination I just talked about, but, rather, came from the first diagnostic section, where, again, there were more than 500 diagnostic terms, three codes for acne out of 91 codes, and, in fact, if you looked at everyone who had a physical diagnosis finding of active acne and,

therefore, should have had a coding of one of the three codes for acne, only 48 percent were so coded.

So more than half the patients who had active acne were not given a diagnostic code and, again, examiner performance varied widely, with some people reaching perfection -- in fact, a few exceeding 100 percent -- and, on average, less than half being coded.

Not only was there substantial undercoding of the physical examination findings in the diagnostic section, which was used by the FDA, but miscoding was even more of a problem. Properly coded, I think, as you can see from the previous slide, that any person with severe acne should have been coded as cystic acne, in fact, only 5 percent of the women on examination said to have severe acne, which includes cysts and scarring and is disfiguring, were given the code of cystic acne.

Sixty percent were given the code of acne vulgaris and 20 percent were given no acne code, this being significantly less than the overall undercoding, but, still, we see that when examiners, which one might understand -- if you have three codes to choose from and you have to remember 90 codes, you probably remember the most prevalent relevant code, acne vulgaris, and do not remember 714180, cystic acne, very often.

(Slide)

In fact, the criteria used in NHANES to define severity of acne differ from currently accepted standards of care as have been recently put forward by the American Academy of Dermatology, and I think are quite different from what those of us who are dermatologists would understand to be severe acne.

(Slide)

For example, if we look at the definition used in NHANES of moderate acne for the physical exam, we see that it includes deeper inflammatory lesions and inflammatory nodules, which some of us would also call cysts, and if you look at patients who were coded as having moderate acne on physical examination, 31 percent had cysts or scars. Most of us believe that people who have cysts and scars do not have moderate acne, but would consider that severe acne in our current lexicon.

(Slide)

Realizing the difference in severity gradings between then and now, let us then look at the projected prevalences of acne in women in 1971-1974 from the examination. Based on physical examination, one-quarter of a million women were projected to have severe acne by the restricted definition used in NHANES, a further 3.8 million women with moderate acne, which includes what I believe would be considered severe today, and many who would not be, and 9.2

million women, aged 15 to 44, with minimal acne.

(Slide)

If you look at a different portion of the physical examination form, essentially those women who had cysts or scars, and, again, look at projected prevalence, you see that nearly a million are projected to have both cysts and scars, indicators of substantial acne involvement, and many of us would say disfiguring acne. An additional 1.7 million had evidence of scars, and many of these were older women whose active acne had gone away, so they did not have acne cysts, but continued to have their scars, and 170,000 were projected to have cysts. These were, in fact, by and large, younger women who may not have yet developed the scarring from the cysts.

(Slide)

I believe, by current clinical standards, a conservative definition of severe acne, as used clinically today, would be using the NHANES categories as those who had severe acne on NHANES or moderate acne with cysts and scars.

(Slide)

Using this as a definition, the projected prevalence of clinically severe acne, as I would use the term, for women was 832,000, for men, 1.3 million in 1974, a male-to-female ratio of 1.6:1, which, incidentally, is identical to the ratio of scarring in a British study of the prevalence of acne, done

before Accutane was available either here or in the U.K., and I think this ratio is a fairly robust one, when one looks at all of the various estimates of the male-to-female ratio.

(Slide)

We all know from medical school or before that incidence equals prevalence divided by average duration.

One must remember that acne severity varies over time and with therapy. The NHANE study was a point-prevalence study in a treated population, and I have talked about that bias, and, therefore, prevalence in an untreated population should be higher. The few data which are available on the duration of moderate to severe acne from one English study done in the early 1980s suggested shorter duration in females than in males, 3.3 average duration for females and 8.2 for males.

(Slide)

One must remember, in talking about the incidence of any severity of acne, that one must only use the prevalence of that same severity of acne. As illustrated here, a typical individual with an up-and-down course over 12 years of acne, if one is talking about this individual as his contribution to the duration of severe acne, one should only look at these three years or, looking at it another way, if this person happened to be counted here in NHANES, he would have been considered moderate, here he would have been considered severe

and, here, and during much of the time, mild. So one has to use the severity-appropriate duration in calculating incidence.

(Slide)

What about if you take all these data together and try to determine what is a likely range in the annual incidence of acne, of women who had severe acne as defined by NHANES, or moderate acne with cysts and scars, which, I would submit, most of us would consider today to be severe.

If one takes the NHANES data, as Dr. Paul Levy has done, and uses both extremes, both the male and female, the three- and the eight-year durations of acne, the 95-percent confidence intervals, as Dr. Levy has calculated, would be that we would expect that somewhere between 50,000 and 327,000 women would, each year, be instant cases of this severity of acne, suggesting, in fact, that, as all of us know, acne which includes cysts and scars and is likely to be quite bothersome and have serious sequelae is hardly a rare phenomenon or orphan disease.

Thank you very much.

CONCLUDING REMARKS OF ROBERT ARMSTRONG, M.D.

DR. ARMSTRONG: I would now like to conclude by bringing the information already presented to the questions the committee has been asked to address.

(Slide)

I would like to begin with comments about the current mode of distribution. As was discussed in the open public section by the pharmacy representative, Accutane is now available in the same way that virtually all other uncontrolled drugs are available in the United States, so this is the current normal distribution system with the advantages that we believe it has maintained.

First, it keeps informed patients and physicians in the position of responsibility for the decision to use Accutane, and when we speak about informed patients and physicians, we mean fully informed about the potential risks and the need to address those risks, as we have outlined through the pregnancy prevention program earlier in the day.

(Slide)

Secondly, the current distribution system does a great deal to maintain patient confidentiality. It is not compromised in the way that a mandatory registration program would be.

(Slide)

The current normal distribution system avoids coercion of patients by making availability of the drug contingent upon acts which they may not wish to do.

(Slide)

It also maintains access to an extraordinarily effective drug for women -- and also men -- and I point out

that some 60 to 70 percent of patients who are taking Accutane are not at risk for birth defects either because they are males or they are women who are not of childbearing potential.

(Slide)

The availability of the drug also avoids a pressure for drug diversion or sharing of drug.

(Slide)

And, similarly, it does not provide a motivation for developing a black market in or imports of isotretinoin.

(Slide)

One of the questions has to do with making changes in labeling or packaging. Here I would submit that efforts that Roche has made over the years have demonstrated a commitment to making changes that would promote the appropriate use and avoidance of pregnancy exposures and birth defects, and clearly that commitment is still active today.

There are several labeling changes which might be considered, and we have three which we would like advice from the committees on. First: Would it be reasonable to provide an alternative of using either urine or serum for doing the base-line pregnancy test? Much has been made of the number of patients who were tested using serum and less attention has been paid to the patients who were tested using urine.

The literature which has been reviewed by us over the past several months indicates to us that urine pregnancy

tests, in the current technology, are as good and perhaps better than serum tests and certainly would offer advantages of cost and convenience for testing to be done by the clinicians in their offices.

We would also be very interested in having any recommendations from the committees of ways to increase contraceptive efficacy.

We would, finally, like input from the committees on the possibility that recommending patients get their prescriptions only after the start of their menstrual periods might be useful to avoid some of the kinds of pregnancy exposures that Dr. Dai discussed earlier.

(Slide)

In conclusion, I would like to emphasize that we do not know everything about Accutane users. We do know a great deal, and Dr. Mitchell has gone into considerable detail about what we know of the patients who participated in the SEU study and what we do not know about the patients who have not participated.

But what I can say with confidence is that the SEU survey has documented that thousands of physicians and patients have used Accutane correctly, thereby obtaining the benefits of treatment while avoiding both pregnancy and birth defects. Also, from the SEU survey participants it is quite clear that patient-education efforts have been extraordinarily

effective and, indeed, that is not contradicted by the group of patients that Dr. Dai discussed who had the unfortunate experience of contraceptive failure, although those patients also had been informed of the importance of avoiding pregnancy.

(Slide)

Next we would point out that there has been a substantial decline in the number of reported birth defects since 1983-1984, and since 1988 the number has remained at five or fewer annually, although we recognize that that number may increase as the SEU survey follow-up is completed and as additional cases may be identified. We do, for the reasons which have already been outlined, believe that the majority of these birth defects are, however, reported to us.

(Slide)

Finally, I would point out that the use of Accutane by women has declined by almost half in 1990 compared to 1983, and that this current usage corresponds to less than one dermatologist treating one patient per month as the actual amount of drug being used.

I know that we have presented a great deal of information in a relatively short period of time and that there may well be questions which the committees would like to pose to us or to any of the people who have already spoken, and certainly we would be happy to address those at the

appropriate time.

Thank you very much.

DR. DAVIDSON: Dr. Roubein has some announcements about lunch.

(Administrative announcements)

DR. DAVIDSON: We will break now for 20 minutes and begin at 10:50.

(A brief recess was taken.)

DR. DAVIDSON: I think we are appropriately recomposed at the moment so that we can begin.

The presentation by the FDA will be introduced by Dr. Lumpkin.

PRESENTATION OF THE FDA

PRESENTATION BY MURRAY LUMPKIN, M.D.

DR. LUMPKIN: Good morning, ladies and gentlemen: During the next period of time several members of the FDA staff will be presenting various pieces of data to you and to the committee for your consideration.

The way we plan to organize our section of the program this morning is as follows. I will be speaking on behalf of the Division of Antiinfective Drug Products and will offer a few comments that should not take a great deal of time. Following my presentation, Dr. Chuck Anello, who is the director of the Office of Epidemiology and Biostatistics here at the agency, will be presenting a program using various

members of his staff and consultants to address many of the issues that you just heard during the Roche presentation and to present their perspectives on those issues.

Then, finally, Dr. Carl Peck, who is our Center director, will offer some final, concluding comments at the very end of the FDA presentation.

As you are all aware, the Division of Antiinfective Drug Products is the division within the Center for Drug Evaluation and Research with the responsibility for the continuing regulation and oversight of Accutane. As you heard this morning, historically, this oversight process has taken two major routes since the approval of Accutane in the early 1980s.

Initially, the major thrust of our efforts was to improve the professional labeling and packaging of the product so that physicians and patients would be fully informed of the various risks associated with the product, especially the teratogenic risks associated with the use of the product during pregnancy.

Yearly review and updating of the label have occurred over the past decade to the point where I believe we would all agree that Accutane is one of the most explicitly labeled products on the American market today.

A second thrust of our oversight has been an effort to engage Roche in a professional education program aimed at

American physicians to further inform them of the risks of the product and the proper approved usage of this product. The efforts Roche has made in direct educational interactions with health professionals and in their professional advertising have been reviewed several times in the past with these advisory committees, as was done again this morning.

I think we would all agree that these efforts in many respects have been unprecedented and they have been pursued by Roche in a commendable good-faith effort to meet the recommendations and requirements of these committees and of the agency as a whole.

However, due to the time frames in which these educational programs have been implemented, this will be the first year we have really any possibility of determining to what extent these programs have accomplished their intended goals.

We in the Division of Antiinfective Drug Products are sensitive to the complex and diverse issues that have been raised regarding Accutane. The continuing review of Accutane over these years in open public advisory committee hearings has allowed a very broad spectrum of national input into the regulation of this drug.

The Division continues to feel that this forum offers the most effective mechanism to allow full and free expression of opinion. Likewise, because of its public

nature, it prevents any one person or any one group from projecting a bias in such a way as to determine the ultimate outcome, and we believe this is the healthy, appropriate way to approach these issues.

While we recognize that the process can be and has been at times highly charged, we also recognize that such is probably necessary, given the importance of the issues raised by the use of this product and the lack of a national consensus regarding some of the underlying issues.

So today you members of the committee are being asked again to advise us on the wisdom of several regulatory options which are available to my Division at this point in time. You are being asked whether you believe even further labeling changes are warranted and, if so, what they might be. You are being asked whether you think further educational efforts are warranted and, if so, how should they be orchestrated?

You are being asked to evaluate whether, after you look at all of the labeling changes of the past decade and all of the educational efforts are taken into consideration, you believe that traditional access to the drug is no longer acceptable from a risk-benefit perspective and only a restricted distribution scheme would be able to accomplish the goal of providing an admittedly effective drug to those who clearly require it, but diminishing the accompanying risk to

an acceptable level.

Or perhaps, after you look at the data, you will view them from a completely different perspective and say that, indeed, there is a large segment of the American population which is not at risk for the teratogenic effects and who are benefited a great deal by this drug.

When you look at the efforts of the sponsor and the efforts of the agency to adequately inform those who are at risk, you perhaps will conclude that, indeed, the sponsor and the agency have fulfilled their responsibilities and the responsibility at this point for assessing risk-benefit is appropriately that of the practitioner and his or her patient.

I have no idea how you are going to view this. Clearly, depending on one's own preference, each of these possibilities has its own merits and its own detriments. The Division of Antiinfective Drug Products is not here today to try to convince you of the wisdom of any of these approaches. That is not our intent and clearly it is not our place in this forum.

We come to this meeting with no preconceived notions regarding these options, all of which are very much on the table for discussion, as far as we are concerned. We are here to listen to the comments of the general public, to listen to the comments of the sponsor, to listen to the comments of our various FDA support groups, and, most importantly, to listen

to the discussions of you, our advisory committee members, and then to garner the expertise and advice you, the advisory committees, have to offer us. Your expertise and advice will be invaluable to us as we fulfill our responsibility to regulate this product most appropriately within the context of good medical science, individual rights, and present public law.

We thank you most sincerely for your time today and for your willingness to aid us publicly in this very important responsibility. We especially look forward to your deliberations this afternoon. Again, on behalf of the Division, we thank you all very, very sincerely.

At this point I turn the program over to Dr. Anello.

PRESENTATION OF CHARLES ANELLO, Ph.D.

DR. ANELLO: I am Charles Anello. I am the acting director of the Office of Epidemiology and Biostatistics.

(Transparency)

I think I have, or this office has, for a goal one question that we want to address: To assess the impact of the pregnancy prevention program on use, pregnancy exposure, and birth defects.

(Transparency)

You have been exposed today to a considerable amount of information from Roche Pharmaceuticals, the Slone Epidemiology Unit, PDS data, National Health and Nutrition

Examination Survey, the Harvard Community Health Plan, and spontaneous reports.

(Transparency)

What we are going to try to do in the next hour is answer some questions, and I will tell you in a minute what those questions are.

With me today are Dr. Stadel, who is the chief of the Epidemiology Branch of the Office, Dr. Paul Levy, who is a consultant to the Office and is chairman and professor at the University of Illinois, Dr. Robert O'Neill, who is the director of the Division of Biometrics, and Dr. Richard Platt of the Harvard Community Health Plan.

I will, after all finish, summarize what all these speakers have said with regard to the following six questions.

(Transparency)

We are going to basically take all this information that you have heard today and attempt to answer six questions:

How many new Accutane prescriptions were issued in 1990 to women 12 to 44 years of age?

How does this level of prescribing relate to what is expected from the NHANES survey?

What is the evidence for a change in prescribing during the period of 1988 to 1990?

Are only women with severe acne being treated with Accutane?

(Transparency)

Given the level of prescribing, what is the estimated number of pregnancy exposures each year?

And what has been the impact of this program on pregnancy exposure and birth defects?

Those are the questions we are going to answer, and I would like to start this with Dr. Stadel.

PRESENTATION BY BRUCE STADEL, M.D.

DR. STADEL: As Dr. Anello said, what I am going to try to do is give my perspective on the progress made towards the goals of the pregnancy prevention program.

(Slide)

The first slide uses PDS beta data to give you the annual estimated number of new prescriptions of Accutane to women of reproductive age. The red line represents one of the calculations for the annual incidence of severe recalcitrant cystic acne based upon the work that Dr. Paul Levy will be discussing later.

This particular estimate -- when these data were looked at internally, a variety of different figures were arrived at -- represents what the staff of the Division of the Dermatologic Drug Products felt was the labeled indication, that is, severe acne, and this comes to an incidence of 13,300 cases per year, with 95-percent confidence limits of roughly between 2000 and 24,600 cases.

Dr. Levy will discuss it in greater detail. You can, of course, get much higher incidences if you loosen the definition and include less severe disease. This is the definition which seemed to represent agreement as to what was intended in the drug labeling to the best I can tell.

There was some comment about duration. This was based on a mean duration of eight years. I was not quite sure how to interpret some of the earlier comments, because I recall Dr. Stern seeming to believe that duration was shorter, but in the Slone study 66 percent of the women reported duration of over six years, so I guess I will stick with what I have for my part of the presentation. Dr. Levy will show you what you get if you change both the severity and duration -- and, of course, you can get any figure you want all the way up and down the screen by doing that.

The rest of my presentation focuses on 1988 through 1990. We know that the use of Accutane came down earlier on. Some of this was probably consumption of the prevalence pool from when the drug was introduced, because, of course, at the time of introduction there should have been a prevalence of about eight times the incidence here, that is, 100,000 cases. That had to be consumed in the early period. Then there undoubtedly has been some reduction in response to the publicity and concern over time.

The question, specifically, that I was to address is

the question of what has been going on during the pregnancy prevention program that started in September-October, 1988, so I have used 1988 as the base for my discussion.

(Slide)

The next couple of slides are other measures of general Accutane use which I think are indirectly supportive of my belief that there has not been a whole lot of change in the use of Accutane since introduction of the pregnancy prevention program.

These are overall data from the number of prescriptions. The only reason for showing these is that they are different resources, to make sure that something is not lost by focusing only on the PDS beta estimate for new prescriptions to women of reproductive age.

(Slide)

This is another one. This one uses the National Prescription Audit. As you see, these bounce around, but in terms of change across the three years, there is not an impressive difference.

(Slide)

The final one is factory sales, calculated out at treatment courses of 40 mg a day.

Those are my data on drug use. I think they express the concern that we have been asked to address in the Epidemiology Branch, that is, to follow the impact of this

program.

(Slide)

These are our calculations for cumulative enrollment of the Slone survey, cumulative through 1989 and through 1990 for various categories of women, new users 12 to 44 years of age, new users of all ages -- well, there it is going to be almost the same, since 99 percent of the women were 12 to 44, as I understand it -- and total women.

The reason for putting these up is just to give an idea that roughly, say, a third of the national Accutane experience has been encompassed by the Slone survey, and this is important to my comments later on, which pertain to what we do and what we do not know about the other roughly two-thirds of Accutane users.

Based on the data in the report, as I understand it, the overall pregnancy rate for the 1989 cohort is .7 per 100 women years -- that is what I get out of the data (not per 1000 but per 100). That was an Accutane course of 140 days, 33 pregnancies over 4556 women years of treatment from, I believe it was, table 47 in the report. That is a net pregnancy rate of .7. That is a remarkable achievement, as I will be showing you later.

If that is truly the achieved pregnancy rate, it is remarkable. In any case, everything I see leads me to believe the program has resulted in substantial enhancement of

contraceptive usage and effectiveness amongst the women included.

I think the question has to do with representativeness, because this is a volunteer-based study and we know that volunteers in many experiences behave differently from nonvolunteers. I am not sure that various indirect measures like demographic characteristics and so on give me a lot of confidence that that distinguished what a volunteer will do from what a person who says, "I don't want to," will do. Maybe it does. I am just not sure it does. And my job here is, I think, is to try to give some measure of what I think we know and what I think we do not know.

(Slide)

In this slide I have put up some descriptive material from the SEU survey. Most of the women, 82 percent -- most of my slides, by the way, are from the report that we had at the end of 1990. I have updated one slide from the report I got as of May 1. It does not make much difference to these, but it can change some numbers slightly.

This simply gives an idea of various behaviors of the women in the survey, depending on whether they were physician- or package-enrolled. I do not have a lot to say about these, except that they had serum pregnancy tests before Accutane in about two-thirds of the physician-enrolled women, less than half of the package group. It nets out to 46

percent.

(Slide)

That was looked into to see if that was really the case. I guess when I looked at the data that came back I have to say there is some support for the idea that there is pregnancy testing that was not recorded. I do not find it real strong, I do not find it real impressive. I see reason here to say that, well, you went to a hundred dermatologists surveyed, 86 responded, you had 48 saying that the office staff says they do routine serum pregnancy testing. Whether that is good enough is up to you. I just do not find that a real strong difference.

(Slide)

I think the part that expresses my concern from the initial slide about what Accutane is being used for in relation to what it is labeled for is that 40 percent of the women in the Slone survey reported they never had any cysts -- this is ever, not at the time, but ever had, 40 percent reported they never had any cysts -- 20 percent reported they had ever had one or two. I think these things fit with my concern from the initial slide that drug usage is many-fold different from the incidence of recalcitrant cystic acne in women.

(Slide)

One could say, okay, but what does that mean, does

it matter? These are some general figures which have been worked up about compliance with various parts of the labeling. I do not think that they are too important, except to notice, again, there is the summary figure of 46 percent for serum pregnancy tests. I think that is grounds for concern because of some figures I will show you later, talking about how many women may be starting Accutane while they are already pregnant.

On the other hand, I did show earlier that the net pregnancy rate might be on the order of .7, so even though there may not be clients with these other things, the achieved prevention of pregnancy for women in the survey appears to have been really very good.

(Slide)

My next comment is really the last part of what I have to say, because I see this as a big-picture issue, without a lot of detail needed, is to try to figure out, in the women who were not in the Slone study, which I think represented roughly on the order of two-thirds -- maybe it is only a half, but my best figures come closer to two-thirds, these are women who did not volunteer and their physicians did not volunteer, so I thought maybe one should view their contraceptive-failure behavior as more likely that of typical observed rates (I will be showing some published figures for those) and they are a lot higher than the women in the Slone

survey had.

If you wanted to try to estimate nationally the number of pregnancies exposed among women not in the Slone survey, you would have to come up with some idea for how many women started the drug when they were already pregnant and how many women then got pregnant because either they were not using contraceptives or they had contraceptive failure, and I have included those two in the contraceptive failure group.

From the best we can tell up through 1990 from the spontaneous reports to Roche and the SEU survey, varying figures can be arrived at, but they come to the notion that somewhere on the order of 30 percent of all women who get pregnant are pregnant when they start. These are order of magnitude -- that could be 20 percent, it could be 40 percent. We are doing the best we can with the data that we have available. We have a lot of data for women in the survey; we do not have many data about women who are not.

To get the number pregnant because of contraceptive failure, what I have done here is to take the total number of users from the PDS beta data, subtract out the one-third that I have estimated to be in the Slone survey, then take five months as the average duration of treatment, so take the number minus the third in the Slone survey times five months to get the women years of exposure among women not in the survey.

Then, if you summate that across the known method-specific failure rate and the method-specific distribution of contraception in the population, you get some idea of how many pregnancies you would expect to occur. That is, if you have a use failure of oral contraceptives published as about 3 percent, that would be here, and then you would have whatever fraction in the population would be in here, and you do that for each method, the failure rate and the proportion.

Since I do not really know the distribution of contraception among U.S. women generally who are using Accutane outside the Slone survey, we used two figures. One is the published data from the National Survey of Family Growth. These are data on the general distribution of contraception in the U.S. and we put that at one pole (and we said the women using Accutane are probably doing better than that). At the other pole we put the contraceptive distribution of women in the Slone survey, and we thought women who are not in the survey probably are not doing quite that well. The truth is probably somewhere in-between.

(Slide)

The figures used to do the calculations -- these are published data actually taken from a nice review article, "Medical Progress on Contraception" that Dan Michele did in The New England Journal of Medicine in 1989, March 23, and it cites the literature experience and the National Survey of

Family Growth, and many studies on contraceptive failure -- these are general figures from the literature of lowest expected values under optimal conditions and typically observed values across broad segments of the population.

If you remember, I said that the pregnancy rate in the Slone survey was about .7 per 100, so that is very good. That means that you have got to have been right up in this area. On the other hand, the typical observed rates in the United States are not at that level; they are more on this level.

On oral contraceptives, it may surprise some people, but it is true that in broad study experience the failure rate the first year is about 3 percent. We did not update it, but this has recently been revised upwards by Jackie Forst at the Guttmacher Institute in New York based upon unreported pregnancy termination which has to be put into the calculation, and when they did that, they upped this to between 5 and 6 percent. I have not seen reaction to that article, so we did not incorporate it and stayed with the more conservative values.

The point to make is that common experience with contraception involves substantial failure rates.

(Slide)

We went to the National Survey of Family Growth distribution of contraception and the Slone survey

distribution to get some figures, and when you compile these together the way I described initially, the order of magnitude is that there may be somewhere on the order of 1000 to around 3000 pregnancies exposed to Accutane annually among women who are not in the Slone survey. That is an order-of-magnitude figure; I will not argue that it is accurate. It is the best we can do based on the information that is available to us, but I think it has some perspective with regard to reporting.

There has been a lot of talk about what is and what is not likely to be reported, and I think there is some plausibility to the argument that it does not seem like there would be the same vast underreporting of birth defects, there is an argument that says there would not seem to be that, as there does seem to be for many conditions.

We did, as was noted, send out a mailing to about 1600 maternal and child health specialists. We got back one report, it was a case which occurred in Europe. So for what that is worth, we did not turn up a lot. It was not a programmatic effort on the scope of the Slone survey; we did what we could with a very limited base.

It is also my understanding the CDC has done some study of mothers of children with Accutane-like birth defects and has not turned up, thus far, any new ones. I do not know what the state of that work is. My understanding is they plan to continue it, because they are concerned, as we are, that it

is hard to believe, given the general experience with reporting, that there might not be a problem.

With pregnancy exposure, however, the reasoning goes differently. I do not have any trouble at all thinking that only 44 pregnancy exposures out of a thousand might be reported. That is four out of a hundred, a 4-percent reporting rate, for something which of itself, unless it has some problems, would not be considered something important to report.

I have difficulty seeing a compelling argument that this rate of reporting largely discounts my estimate for what might be happening -- and I emphasize "might" be happening. I am trying to fill in unknown areas with estimates, because I do not have data. I do not have hard follow-up for all women treated with Accutane (I only have it for about a third).

In any case, we have 44 exposures reported in 1988, with four defects, and 53 in 1989, with five defects, back to 44 in 1990, one defect thus far. As of the report that came to us May 1 from Roche, I understand there were six more pregnancies exposed in 1990, so these have to be well along now. I do not know the outcome of these. I do not know what that is, and I would be interested to know what that is. As I understand, there has been one thus far, it was mentioned, an elective pregnancy termination.

Dr. Armstrong, in commenting on this, said that they believe that the majority of birth defects have been reported. Does that mean that there might be three unreported ones? That is what I guess the majority would mean. I do not know. I do not know what reporting is on this. My estimate of pregnancy exposure leads me to the concern that there could be more of an unknown problem nationally than we are aware of at the present time, and that is my message in trying to respond to the overall picture.

What is occurring nationally with Accutane? What do we know and what do we not know? I think we know that the women in the Slone survey appear to have had a very good experience with regard to pregnancy exposure, and maybe that gives you an idea of how well you can do when you have people enrolled in an active program.

My estimates maybe give you the other extreme. I originated from the West Coast and these kinds of concerns, for those of you who do not come from there, they do tend to march westward -- you can see that in the reduction in dosage in contraceptives in the early years of concern, the reaction to the information was later, in general, in the western half of the country than in the eastern half.

Dr. Platt will be speaking to us about the Harvard Community Health Plan, and I think in that context what he will be describing probably represents what, in a very

premier-level HMO with a lot of Harvard-affiliated professors, a lot of attention to what is going on nationally, I think his report gives an idea of what you can expect as the leading edge of change in a population-based study.

My figures, I think, give you what concern might be occurring elsewhere in the country, and the Slone survey, I think, tells you what happens, perhaps, if you actively enroll women in a program where there is a real feedback exchange.

Thank you very much.

DR. ANELLO: Are there any questions for Dr. Stadel before we go on?

(No response)

Dr. Stern gave a reanalysis of the NHANES data. We had asked Dr. Paul Levy to take a look at what Dr. Stern had analyzed and, also, we consulted with the Division of Antiinfective Drugs, particularly Dr. Phyllis Hume is in the audience here, about what was intended by the label with regard to severe cystic acne.

I would now like to have Dr. Levy give his presentation.

PRESENTATION BY PAUL LEVY, PH.D.

DR. LEVY: Thank you.

(Transparency)

I am going to talk about some reanalysis of the NHANES-I data using, I think, the same tapes that Dr. Stern