In order to validate the pregnancy rates obtained from the Accutane survey, we took a look at two sources. The first source is the United Healthcare database, one of the largest health care databases available. We observed that there was no significant difference between the pregnancy reporting rates compared to the Accutane survey.

Next we took a look at data from a phase III clinical trial which was similar with about 4 per 1,000 patients exposed. But this goes to show that even in the setting of a clinical trial, the most controlled, mandatory environment, that patients still got pregnant.

In summary, you can see the overall pregnancy rate from the Accutane survey is 2.8 per 1,000 patients, and that this again is supported by additional evidence outside of Slone. Also, the pregnancy rate has been declining since the initiation of the pregnancy prevention program.

In all our discussions going forward, we will be using the rate of 3 per 1,000 patients exposed.

In conclusion, the evidence presented above indicates that for every 1,000 women on Accutane, approximately 997 avoided becoming pregnant.

Now, I'd like to introduce Dr. Allen Mitchell, who will now present the Accutane survey which we consider

a critical component to the pregnancy prevention program.

Thank you.

DR. MITCHELL: Thank you, Dr. LaFlore. It's a pleasure to be back at the committee after many years of absence. My name is Allen Mitchell. I'm in charge of the Accutane survey. This is an activity, as you've heard, that began in 1989. It grew out of our long-standing, 25-year history of interest in the research as to etiology and prevention of birth defects, and the experience of Accutane led to us becoming involved in a vaguely similar activity with respect to thalidomide and the STEPS program.

What I'm going to do this morning is to provide an overview of the survey and its results, and obviously take any questions that might come along. I suspect there will be some.

First of all, the pregnancy prevention program was introduced in the fall of 1988 as a multi-component program aimed at female patients and their physicians, and it was recognized then and now as an unprecedented and novel approach.

The question of course is, does the PPP work? What we set out to do as an independent effort funded by Roche is to enroll and follow a cohort of women who were exposed to Accutane. This is not a pregnancy registry, as many people are familiar with pregnancy registries. We are

identifying users of Accutane.

The survey, as I mentioned, is sponsored by the manufacturer with the Slone epidemiology unit responsible for the design and protocol, data collection, data processing, data analysis. This activity is operated with the very real guidance of an independent advisory committee. That committee is listed here. I do want to mention that Dr. Paul Stolley, who served as our chairman, resigned as chair in July of this year because he has joined the FDA as a senior consultant. The remaining members of the committee and the ex officio observers from NIH and CDC continue.

The objectives of the survey are to assess compliance with the pregnancy prevention program, and specifically to identify the awareness of the teratogenic risk, patient and physician behavior, pregnancy rate based on a denominator as opposed to simply spontaneous reports, pregnancy outcome in terms of the fate of the pregnancies. Our study was not designed to identify the proportion of exposed pregnancies that result in malformed births. And further, to identify risk factors for pregnancy.

At the outset and to this day, we have noted that there are limitations to this approach, as there are to virtually any kind of approach. First of all, we didn't have the benefit of pilot testing. This was implemented

without an opportunity to pilot test.

Clearly there is no ability to make a pre- and post-comparison because we don't have equivalent data from the years preceding the survey.

There is no definition of what success is. Is success zero pregnancy? Is it a lower rate of pregnancy? And if it's a lower rate of pregnancy, how low? I think everyone would agree that we would expect and hope to see a rate of pregnancy that was considerably lower than the general population rate, but beyond that I don't think there has been to date a formal definition of what constitutes success.

The survey itself is an intervention, and we'll talk about that in a little bit.

And finally, and something that has been the focus of much attention, is the survey is based on voluntary enrollment, and from the very beginning we've had concerns about whether the population of women who enroll in the survey represent women in general who are taking Accutane.

Let me describe the design because it bears on the results. First of all, the time period of interest was the early part. The left side of this figure is the period of Accutane treatment which was anticipated to be on average 5 months, which is what it turned out to be. And

we included another 6 months after completion of therapy as an opportunity to identify potential pregnancies within the first two trimesters.

Because it was a voluntary survey, we needed to figure out ways to encourage enrollment, and we used three basic principles. One is to present multiple different opportunities, to keep it simple, and to provide a payment for the women's efforts. And let me go through the three enrollment opportunities that we considered and implemented.

First was to have women enroll through the prescribing physician. Since all prescriptions presumably originate with the physician, this is logistically feasible, and a physician who encourages a woman to enroll provides a strong incentive for that woman to enroll.

Second is a toll-free telephone call which is simple, quick and familiar.

Third, we developed the package generated enrollment opportunity which is both unique and unprecedented, and we used the principles basically of direct-to-patient approach in the package generated opportunity in which each medication package includes an enrollment form. So, every time a female patient opens -- and male patient for that matter -- opens a package of Accutane, there is an enrollment form in there.

The objective here was to bypass the physician, and the hope was that this approach could preferentially target women who were not encouraged to enroll in the survey by their physician, who may be relatively noncompliant, or who were simply attracted by the payment. As you'll hear a bit later, we think that some of those objectives might have been met.

We've now enrolled women. How do we follow them? Again, there's more than one way to do it, and there are tradeoffs depending on which approach one takes.

One could, first of all, try to follow women frequently during and after the course of therapy. This has the advantage of avoiding recall bias because women are providing information presumably in real time. It has the disadvantage in that it could conceivably affect the outcome beyond the PPP itself, which is the approach we were trying to measure.

An alternative is to follow up women relatively infrequently, following them only after treatment was completed once they've enrolled. The advantage here is that it avoids an intervention beyond the PPP. The disadvantage is that it offers the potential opportunity for recall bias.

We used both, and the survey design is presented in this slide. As I mentioned, women can enroll

through any of three different methods. Once the enrollment is received, within 48 hours a check for $10 is sent to the women, and the women are randomized to be followed by one of the two follow-up methods. 5,000 women a year are assigned to be followed on a random basis, through what we call the DAT, the during and after treatment follow-up. That includes a questionnaire. In the early years, it was a telephone call; in the later years, a questionnaire at the onset of therapy, in the midst of therapy, and 6 months or more following completion of therapy.

The remaining women beyond the 5,000 who were randomized to be followed in the DAT arm, are followed in what we call the AT arm, where there is a tracking questionnaire, and only a tracking questionnaire sent at about 6 months, after most women have completed their course of therapy. And then a final questionnaire comparable to the DAT questionnaire is provided to the women at 6 months or more after their course of therapy.

Now, these different approaches provide different opportunities to collect information, and these are only examples. We have tried to collect information on patient characteristics, patient knowledge, compliance, and pregnancy occurrence.

As you can see, the DAT questionnaire, because

it's frequent, provides many more opportunities to collect information than the AT, but both questionnaires ask about pregnancy testing, contraception, and pregnancy occurrence. This information is directly solicited from the women who participate.

As you might guess, because information comes from different sources and different numbers of women, the denominators in the presentation that follows vary according to which survey arm is being represented.

But let's turn to the results of the survey and first consider enrollments themselves. Enrollments have increased from year to year with a low of approximately 20,000 in the first year, to the most recent completed year of 1999, where we have 53,000-52,000 enrollments. Our projection is that for year 2000 we'll have roughly 55,000 enrollments. To date then, we've enrolled close to 500,000, close to half a million women, who have taken the drug.

It's interesting and important to recognize that the vast majority of women who enroll in the survey don't do it through the doctor and don't do it through the toll-free number, but do it through the medication package, the direct-to-consumer, if you will, the direct-to-patient approach.

What about follow-up? First, we'll consider

the during and after treatment approach, the follow-up approach, in which we've enrolled 61,000 women approximately, to date. And as I mentioned, in the first 5 years of the survey women were followed by telephone. It's striking to note that the three opportunities for telephone interview gave us follow-ups of 98 percent, 98 percent and 93 percent. That's remarkably high.

In the more recent 5 years where we've used mail questionnaires to conduct follow-up, we've seen comparable follow-up rates, 98 percent, 98 percent, 97 percent.

In the after-treatment arm, where women aren't approached with any questions for about 11 months, we've enrolled 433,000, and of those, follow-up rates have ranged from 80 to 86 percent, still very impressive follow-up rates for a survey of this kind.

What are the demographic characteristics of the women who have enrolled in the survey? Well, the average age is 25.6 years. The median is 24, but this has changed over time, as has been suggested by previous presentations, with respect to sales. So, the average age at the onset of the activity was somewhere between 26.5 and 27 years, and the age at present is approximately 25 years. I've indicated recent data that are incomplete with a cross-hatch, so every time you'll see that, it's to indicate that

these data are incomplete and should be regarded with some caution.

Who are the women? Their educational distribution indicates that approximately 70 percent have had some college education at least. 90 percent have a prescriber who's a dermatologist, and the majority of the remaining women have been prescribed the drug by general practitioners or family practitioners.

90 percent of the women reported that they previously received antibiotics. A small proportion received oral vitamin A. About 80 percent/70 percent had received Retin-A and benzoyl peroxide. These were relatively constant over time, with the exception of Retin-A, where use has declined somewhat over the years and has not been replaced, by any way we can identify, by other topical retinoids.

What was the pregnancy risk category, what was the pregnancy risk, if you will, of the women who enrolled in the survey? This represents the last 5 years of data, for 28,000 women.

3 percent reported that they had had a hysterectomy or were post-menopausal. Incidentally, women who report that they're infertile without any other evidence to support it are not included in this group. They are included in other groups.

57 percent reported that they were not sexually active, and 40 percent reported that they were sexually active. These data have been reflected before in Dr. Vega's presentation.

Among those who were not sexually active, 44 percent were using birth control, despite the fact that they were reportedly not sexually active, and among those who were sexually active, 98 percent were using birth control.

What did the women know? 92 percent reported that they had received the patient brochure; 42 percent, the true-false test; and 53 percent, the birth control brochure.

43 percent reported that they knew the drug could cause miscarriage, and 99 percent reported that they knew the drug could cause birth defects. Again, these have remained constant over time.

What about compliance? 99 percent were told to avoid pregnancy. 77 percent reported signing a consent form.

And I need to point out here the question that came up earlier about the process of consent, a very relevant one. What we know is that the women reported signing a consent form. We don't know whether the process was a good process or a bad process, but we also don't know

whether they were truly informed but didn't sign a consent. We can only make some surmises from other data.

67 percent reported that they postponed Accutane until pregnancy test results came back, and 57 percent reported postponing Accutane until their next menstrual period.

This slide presents those four areas of compliance over time, and the intention here is to indicate that, over the last 5 years, there's really been no apparent decay in any of these measures, and there is some suggestion that at least for signing a consent form, that there may be a slight increase, certainly nothing dramatic. But no evidence of decay in these areas of compliance.

And in terms of pregnancy testing, we've mentioned that 76 percent of women who reported having a pregnancy test, the majority of those women had a serum pregnancy test.

Again, in the last 5 years pregnancy testing before starting Accutane by enrollment year has remained fairly constant, at about 75 percent, with incomplete data for the last year, but it wasn't always this way. Let me go back now and talk about levels of knowledge and compliance at the onset of therapy back in the first 2 years of the survey, when we had only 9,000 women enrolled.

At that time, the questions were slightly

different because they were asked by telephone. 78 percent of women reported that they had been instructed by their physician to wait until the pregnancy test result came in. 63 percent reported that they were told to wait until the next menstrual period, and 60 percent -- only 60 percent -- reported any pregnancy test before therapy.

Those data were in our regular quarterly reports provided both to Roche and to FDA, and this information prompted Roche to change the medication package.

The original medication package is displayed here. There is no need to try to read it. In fact, one of the points of the slide is that there is a lot of information here that is not terribly clear, and it was changed to this, which was a fairly dramatic change, with bold red, warning to female patients with what we call the four "musts", referring to those areas of non-compliance that had been identified in the survey. We now present the 2 years of follow-up, 2 years preceding and 2 years following. What we saw is, for each of these measures of compliance, increases in the area of 10 to 20 percent, relative increases in compliance, as a result of that change in the medication package.

When we look at compliance with our pregnancy prevention plan, it's important to consider contraceptive

status according to women's age. This slide presents non-contraceptors by age group, and not surprisingly, the largest rate, the largest proportion of non-contraceptors occurs in the youngest women, and it varies with age, as is shown here. But it's also important to point out that the women who report being sexually active, even though they're not contracepting, is a small fraction of each of the age groups.

If we look at surgical sterility, we see what we would expect to see, an age-related trend.

If we look at non-surgical contraception, typical forms of contraception that most of us think of, we see the distribution that reflects the nature of childbearing years, that non-surgical contraception is most frequently used among women in their typical reproductive years, rather than at the extremes.

The proportion of women who are non-surgical contraceptors has increased somewhat in the survey years in the last 5 years, and among the non-surgical contraceptors, the proportion who are using the oral contraceptive, which is one of the more effective means of contraception, has also increased over the years.

Contraceptors using two or more methods of birth control. Again, as was the case with non-surgical forms of birth control, the highest proportions are among

the women who are in their active reproductive years, and the proportion of women reporting two or more methods has increased slightly over the last 5 years.

Now, we've shown, and it's been remarked on, that there are levels of noncompliance which could be worrisome, and there is no question about that. But I think it's important to look at the proportion of the most at-risk women who are noncompliant with pregnancy testing and waiting to start Accutane.

If we look at the 27,000 women roughly who were in the DAT 1 follow-up arm, that population, 24 percent reported no pregnancy test before starting Accutane. That's been described. Of those women, 60 percent did not wait until their next menstrual period, and of those, 1,500 or so, or 39 percent, were sexually active, but only 39 percent were sexually active not using birth control. Thus, among the 27,439 women in this follow-up arm, 0.1 percent were sexually active, not using birth control, had no pregnancy test, and did not wait until their menstrual period before beginning Accutane.

Now, let's look at the obvious and most important outcome of the pregnancy prevention program, pregnancies. Between 1989 and 1999, we have completed follow-up on approximately 350,000 women. As you recall, follow-up doesn't really begin until 11 months after the

course has been initiated. Among those, 1,019 pregnancies were reported to this survey. The number of pregnancies per year has remained relatively constant over time. Again, 1999 represents incomplete reporting, and to some extent 1998 as well, but we would expect this number to increase as the follow-up increases.

10 percent of the women who were pregnant at the start of treatment, 23 percent reported no contraceptive use, and 66 percent reported contraceptive failure, reinforcing the point that contraception is not a perfect science, and that there are contraceptive failures among women who use contraception.

What are the outcomes of these exposed pregnancies? Two-thirds resulted in a therapeutic abortion, 17 percent in a spontaneous abortion, 11 percent a liveborn infant, three percent ectopic, and 1 percent were unknown. Only 1 percent were unknown.

I need to comment here that in the presentation earlier in the day it was mentioned that there was a 13 percent rate of major malformations among the children, the liveborn children who were followed, and that's correct. However, it also needs to be borne in mind that 60 percent of the mothers who had liveborn infants following Accutane exposures refused to provide medical information or access to medical information. One cannot, as one would argue,

make assumptions from a 40 percent sample as to what the malformation rate is. I think it's quite credible, as a matter of fact, and we have anecdotal information from our telephone calls to suggest, that women who have had an Accutane-exposed pregnancy knew what the risks are to a large extent, and were not interested in going further into that problem if they had a child who had a malformation.

We agree that the expected rate of malformation is what Dr. Lammer's early studies had showed, approximately 25 percent, and we find no difficulty in understanding why we would have a lower malformation rate. The malformation rate is very different from the pregnancy rate, and I want to emphasize that. In the pregnancy rate, as you recall, we had follow-up ranging from 80 to 98 percent.

Let's turn our attention to the pregnancy rate itself. During Accutane treatment, here we're constraining these samples to the duration of use less than 1 year, which is the vast majority of women, giving us a denominator of 340,000, with a numerator of 992. The rate per 1,000 Accutane courses, which we felt was a clinically meaningfully way of expressing this information, was 2.8. The rate per 1,000 person-years, which is placed here for the benefit of demographers, is 7.4

The pregnancy rates during Accutane treatment

by age are presented in this slide. The highest rate is among women in ages 25 to 34, and on either side of that age, rates decline, so that among the youngest women the rate is one, among the oldest women the rate is 0.5.

What's happened to the pregnancy rate over time? This is 1,000 person courses. It has declined, as has been noted, from somewhere in the neighborhood of 3.5 to 4 in the early years, to the most recent complete year of 1998. Now, as you saw in the briefing materials, 1999 we appear to have a rate of close to 3.5. This is following a pattern that we've observed before, specifically for 1996. If you recall the survey -- well, you don't recall because I haven't told you yet, but the survey captures information on pregnancies before it's captured all the denominator information. So, it's not unusual, and the almost exact same rate was observed in 1996. Early on in the data collection for a given year, you can see a rate that's higher than it ultimately is when follow-up is completed.

Well, what are the pregnancy rates by contraceptive method? What we see here are a number of things. First of all, we see a rank order of failure rates, or pregnancy rates, if you will, that's compatible with what one would expect. We're talking about order now. So that rhythm and condom have the highest rates of use.

We still see pregnancies for tubal ligation and for vasectomy, so even so-called surgical sterility can result in pregnancies. For the largest group of women in the survey using the oral contraceptive, almost 100,000 women, we see a rate of 2.5 per 1,000 courses. One expects to see oral contraceptive failures, particularly when you see such large groups of women using the pill.

We also see among the women who reported not using any contraception a rate of 1.7. A finite rate, for sure, but certainly not something that suggests that women who are not using contraception are at surprisingly high risk.

Let's turn to two critical questions: Are the data valid, and are they representative? When we talk about validity in any epidemiologic activity, we need to consider follow-up rates. If we have very low follow-up rates, as we do for following pregnancies resulting in liveborns, we have concerns. Here we find that follow-up rates to the survey are extremely high. As we mentioned, in the AT arm it's 80 to 86 percent, in the DAT arm it's in the high 90s.

Secondly, the responses are remarkably consistent, whether women are followed in the AT arm or the DAT arm. They reflect similar rates of knowledge, behaviors, and indeed their pregnancy rates are quite

similar. So, within the survey we see pregnancy rates that are similar irrespective of the follow-up methods, one being intensive, the other being less intensive.

How does this relate externally in terms of validity to the U.S. population? If one looks at the NCHS data, the government data, and we'll refer to NSFG as well, if we look at the women in the Accutane survey versus the general U.S. female population, and now express pregnancy rates for 1,000 women-years, we find that the Accutane survey rate of 7.4 is about 7 percent of the U.S. population rate.

Does that make sense? Is this difference reasonable? One of the concerns we hear is that the information in the survey may not be plausible, but I'd like to show you some data that suggest to us that perhaps it is.

If we look at the comparison between women in the survey and the U.S. population, and look at the proportion of sexually active not using contraception, among different groups, less than 1 percent or 1 percent report being sexually active and not using contraception. In the U.S. population, those rates are considerably higher, 5- to 7- to 10-fold higher.

If we look among contraceptors, the proportion using the birth control pill, in each age group we find

that women in the survey are disproportionately more frequently using the pill than are women in the general population.

Now, I'd like to suggest that this isn't just a difference in proportions. It's actually a difference in other factors. James Trussell and his colleagues have looked at major factors associated with successful contraception, and the four major factors they've identified are age, which really predicts coital frequently and fecundity, education, duration of method use, and motivation.

Now, we don't have information on the details of sexual activity. We do know that our population is uncharacteristically well educated, and we do know that there is probably no more motivated group of women that has ever been studied when it comes to contraception. The information that they report having seen and heard indicates to us that they have unusually high levels of motivation. In fact, we are looking at these women as a new sample of how good contraceptive efficacy can be.

When we look at the contraceptive failure rates in the survey, compared to typical use and perfect use, we find that for those methods that are most subject to user error, we have remarkably high efficacy. In fact, for virtually all methods, we see efficacies that are as good

as or in some cases better than perfect use.

And what needs to be understood is that perfect use is not based on observation. It is based on speculation. The demographers have done an extremely good job in trying to predict how well the method would work if it were used perfectly. But we would venture to argue that if one wants to see how efficacious a given method of birth control can be, come to women who are being placed on Accutane.

Finally, we've talked about the follow-up rates, the responses being consistent. I want to show you some information that we published in the New England Journal in 1995 in terms of the pregnancy rates rebounding after stopping Accutane. What we found when we looked at pregnancy rates and outcomes, during and after therapy with isotretinoin in this sample of 122,000 women, was -- and this time the pregnancy rates were a little higher than they are now -- that during treatment we saw a rate that was approximately 7. This is expressed now as demographers would express it. And in each succeeding month following discontinuation of Accutane, we saw what we call a rebound in pregnancy rates, suggesting strongly to us that pregnancies were not only being reported to us but being deferred into the months following Accutane. And within those pregnancy rates, the proportion of women who sought a

therapeutic abortion changes dramatically from approximately two-thirds that we've described during treatment to approximately 25 to 30 percent in the fourth month following treatment.

Now, let's shift to representativeness. I think it's very important to stress that when we talk about representativeness, we are not talking about whether the Accutane survey represents the population of women in the United States. There is a bit of a catch-22 here because if the PPP were completely effective, one would expect to see a population of Accutane users that is extremely different from the general U.S. population. That is in fact the goal of the PPP that is initiated by Roche and FDA.

What we're talking about when we talk about representativeness is whether the survey population represents the population of women on Accutane. And here, as we indicated early on, we did have concerns at the beginning of the survey that the population might not be representative of the Accutane users.

Unfortunately, we were misquoted earlier in the morning. In our New England Journal report what we said was, we assumed a priori that the women who did not enroll were more likely to be noncompliant and at high risk for pregnancy. On the other hand, women may not enroll

specifically because they are infertile, or in other ways not at risk for pregnancy. So, our own view of the bias that was likely in this survey has been moderated, if not changed, by the data and the comparisons that we've conducted, some of which we'll share with you now.

When we talk about representativeness, we need to answer two questions. What proportion of eligible women enroll in the survey? But the more critical question is, do women in the survey represent the larger population? You could have a 10 percent enrollment rate in theory that is entirely representative, and you could have an 80 percent enrollment rate that is completely unrepresentative. You may have a 20 percent population that is dramatically different and not included in the survey.

So, the real question we need to answer is whether women in the survey represent the larger population of Accutane users, and we use three data sources to try to attack this. I think it's clear to people who have been following this issue, and certainly we have struggled with our own advisory committee, it's very, very difficult to resolve. I think the FDA has made that argument, and we support it. So, what we are showing you is somewhat indirect. It is not what we would like to have, but it is interesting and remarkably consistent.

First of all, in the very early years of the survey Roche conducted a consumer survey where they identified 400 women who were using Accutane, and they found that 60 percent of those women reported enrolling in the survey. We had some concerns about the way that survey was conducted, and so we didn't hang our hat very heavily on that 60 percent and thought that maybe was a little high.

But what is interesting is the comparison in that population among the women who reported enrolling in the survey and the women who didn't. The concern, of course, is that the women who didn't enroll in the survey were at higher risk for pregnancy and were therefore being missed by the survey.

In fact, what we found is that the younger women who tend to be at higher risk seem to enroll in the survey more often than the older women. Education was roughly similar. Sexual activity was higher among the women who enrolled in the survey than among the women who didn't enroll in the survey. When you look at contraceptive methods among the 205 contraceptors who were identified, among the enrolled women, 40 percent were on the pill compared to only 16 percent who were unenrolled.

But with surgical sterilization, which I think we would all agree is associated with the lowest risk of

pregnancy, the distributions were quite different. Among enrolled women, only 44 percent were sterile, whereas among the women who chose not to enroll in the survey, almost two-thirds were surgically sterile, suggesting to us that perhaps women who don't enroll in the survey don't enroll because they don't feel, or their doctors don't feel, that they are at particular risk.

A far better analysis, in our view, was the United Healthcare analysis, and this is to be distinguished from the one you heard about a little earlier. This is something we conducted directly with United Healthcare a few years ago, and it examined a population of over 1.2 million women of reproductive age. This is between 1990 and '96. The health plan was able to identify 5,095 women in that age group who had filled an Accutane prescription in that period of time.

Among that population, using a very sophisticated matching technique, which is not perfect, we concluded that 38.4 percent were definite matches, and another 7.5 percent were probable matches, or around 46 percent in those years, we judged in this large health plan to be enrolled in the survey.

But again, as I mentioned, the rate of enrollment or the proportion of enrollment is not as important as the characteristics of those who enroll and

who don't enroll. What we found, again, is that the women who enrolled in the survey tended to be younger than the women who weren't enrolled.

Interestingly, and supporting some clinical reports, the enrollment rates by age were highest among the youngest women. So, 38 to 41 percent of the women at most risk were enrolling in the survey, whereas women in the ages 50 to 59, for example, only 14 percent enrolled in the survey. Again, this pattern of more enrollment and higher rates of enrollment among women who are presumably at higher risk.

We also sought to pursue this question within the survey data, our own survey data as well. Of course, the question is whether there is selection bias favoring women at low risk.

If you recall, we indicated that the doctor-generated and package-generated methods of enrollment were designed to recruit different populations of women, and I think we can debate at great length how much these populations differ and in what respect, but I think we can agree that these populations of women who enrolled in the survey -- and remember that this constitutes three-quarters of the enrollment, the direct-to-patient enrollment -- are different. Fewer reported signing a consent, fewer of them had pregnancy testing, and fewer of them were treated by a

dermatologist.

It's also important to note that among women who enrolled by the medication package, only 13 percent reported that they did so because of their doctor's encouragement. And this familiar pattern again, that when we asked women about doctor encouragement to enroll, the highest proportions were among the women at greatest reproductive risk, with the lowest proportions at the tails of the distribution.

In summary, since 1989 almost 500,000 women have enrolled in the survey. Follow-up rates are high. Except for a slight decline in age, demographic characteristics have remained stable. Awareness of the teratogenic risk is high, and compliance with pregnancy testing and contraceptive guidelines is variable, but not decreasing. Pregnancy rates are appreciably lower than the U.S. population and have declined over time. We believe the data to be valid, and we find no evidence that the survey results are not representative.

Now, having said that, there are always ways to improve things. In the next two and final slides I wanted to outline how we, together with Roche, hope to improve the survey activities.

First, we want to increase enrollments. The payment for enrollment began at $10, and over the last

10-11 years inflation has certainly made a difference, so we want to increase the payment. We would like to add a payment upon completion of the survey. We want to work with Roche to modify the doctor-patient enrollment procedures to encourage physicians to more actively recruit women into the survey.

We want to enroll women on multiple courses of Accutane, which for technical reasons has not been done to date.

And we want to increase the power and the value of the DAT follow-up arm, now that we've learned that we are not getting into major problems of recall bias, or other matters of bias, for that sake, between the two follow-up arms, we feel there is some real value in increasing from the 5,000 a year who are randomized to this intensive follow-up to at least 25,000. The objective would be to enroll half the women from the survey in the DAT follow-up so they would be equally distributed in the two follow-up arms, but a minimum of 25,000 women.

We want to modify and expand survey questions about oral contraceptive type, refining the pregnancy risk questions. Frankly, we were intrigued by the question of the informed consent process, and that might be something to inquire about as well.

And we want to initiate regular feedback to

prescribers to encourage them to value the survey and to enroll their patients.

With that I will end and turn the lectern over to Eileen Leach. Thank you.

MS. LEACH: Thank you, Dr. Mitchell.

You've heard previously about a targeted pregnancy prevention program, and I'd like to go through that with you now. The targeted pregnancy prevention program comes from an analysis of the 1988 pregnancy prevention program that you've heard much about today. This program is revised so that the 3 in 1,000 patients who did not avoid pregnancy will be targeted for this program. Also, physicians have reported to us that they are having difficulty assessing and predicting what an individual patient's behavior might be, so we'd like to address that.

But no matter what program we have, we only have one goal, and that goal is to prevent pregnancy.

You've heard previously from the FDA that this drug was launched in 1982, and it was launched as a category X with very strong warnings to avoid pregnancy, which was based on animal data. In subsequent years, as information became available, the package insert was revised. In 1988 we created the first risk management program for pregnancy prevention, called the Pregnancy Prevention Program for Women on Accutane.

The elements of the label change in 1988 indicated that pregnancy tests should be required 7 days before starting Accutane, and that the patient should use two reliable forms of birth control and begin therapy on the second or third day of the next menses. One month of prescription was indicated for female patients, and a monthly pregnancy test and monthly contraceptive counseling was indicated.

In addition to the label, we created a blister package, as seen here, which had an Avoid Pregnancy logo at every single pill site. As a woman would push, or even as a man would push his pill through, they had a strong warning to avoid pregnancy.

We also included a black box warnings specifically written for patients, and the black box warnings also included a line drawing of birth defects. This is what is known as the PPP. The original package was a box which contained all of the elements in dividers. And later, because of prescriber information, we changed to a single packet for each patient which contained all the elements that were in the box.

This pregnancy prevention program was meant to assist prescribers in meeting requirements of the label. It was also developed in cooperation with the American College of Obstetrics and Gynecology, and very importantly,

this program initiated the Accutane survey that Dr. Mitchell has just spoken about. As we've been questioned before, it also initiated at that time the Accutane tracking survey.

Dr. Mitchell has told you that 99 percent of the women who are in the survey report that they knew that they should not become pregnant while they were on Accutane therapy. 97 percent of the prescribers tell us that they use at least one component of the pregnancy prevention program, and the pregnancy rate in 1989 was 4 per 1,000, and in 1998 was 2.1 per 1,000, a mark of success.

But what do the patients tell us? What are the things that they want to communicate to us? They want to communicate that there is some confusion about the timing of the pregnancy test, and in fact, sometimes they had false negative tests. Many of them said, and these are the women who became pregnant, said, I didn't wait for the second or third day of my menstrual cycle.

There was misinformation and confusion about contraceptive methods. Some women received more than a one-month supply, and some women reported that they had no monthly pregnancy testing and no contraceptive counseling.

Of the women who became pregnant, there are five reasons that dominate why they became pregnant. Women reported that they had committed to abstinence but were

unsuccessful. Women also reported that they had used ineffective contraception, or when using contraception had used it inconsistently. They also reported that they had some unexpected sexual activity, and some reported that they had failures of their contraceptive method.

Just to put in context, of the women who became pregnant in the United States, from CDC data, 45 percent of those women said, I had a mistimed or unwanted pregnancy. As you've heard before, if you use birth control pill, the most dominant form of contraception in the Accutane group, typically 5 out of 100 women could expect a pregnancy. In contrast, we have 3 pregnancies per 1,000, or a pregnancy rate of 0.3 percent.

91 percent of the women who became pregnant told us that they knew the drug could cause birth defects if used during pregnancy, and the mean age was 26.3 years of age. It is not seen to be a problem. Or it is a problem, but it is not preodminantly young people who are having these difficulties. They are people in the most fertile age of their lives.

But even if you say the numbers are small, it's still terribly concerning because if you expose a fetus to Accutane, it is a known teratogen, and it's concerning because women of childbearing potential are the women who are using Accutane.

Another statistic -- and the data supports this from a survey that we have done -- is that 91 percent of women will tell you they know everything they need to know about contraception. But in that group, 37 percent will select from a list the most ineffective contraception. Clearly, a case for education.

But what do we want out of risk management? What we really want is to select and target those people who are not successful, and we also don't want to negatively impact on compliant patients, or on the current success of the program.

We also wanted to look at the Presidential and Congressional Commission on Risk Assessment which was published in 1997, and look at the risk management model that's been proposed, one that will identify issues and put them in context, assess the risk and the benefits of the drug, identify and analyze which options are available, select a strategy, implement the strategy, and of course, evaluate the strategy. But central to all of this is to be able to engage our partners and other stakeholders.

When we looked at the pregnant women, they fall into four major categories. For 10 percent, there was not enough information available to be able to characterize, but for 14 percent the women reported that they were pregnant at their initial visit. While they were in the

doctor's office, they were already pregnant and either didn't know it or had a pregnancy test that was too early to detect it or didn't have a pregnancy test.

12 percent took a prescription home with them and did not wait to the second or third day of their menstrual cycle and began the medication. We've seen pictures today of women who have this terrible disease, and I can imagine that people would be anxious to move ahead with their therapy.

64 percent became pregnant during therapy. As we've heard, most of them became pregnant in the early part of their therapy, a clear indication where education could really help.

Pregnant at the time of the initial visit and the next menses. Pregnancy testing. The solution for this is pregnancy testing. And Roche has given to its prescribers a urine pregnancy test kit that can be used at any time and given to the patients as often as they wish to give it to them.

For the 64 percent, 11 percent of them reported that they had committed to abstinence but were not able to maintain that abstinence.

34 percent said they failed to use the contraceptive on the perceived date of conception, but note that a third of them were also saying they were only using

one form of contraception.

Half of the patients reported that they had a contraception failure, but 61 percent of them said they were only using one form.

So, what do you do? Here are the provisos. Revise the Accutane labeling for two safe, effective forms of birth control. Obtain negative results from two pregnancy tests, provide the urine pregnancy test kits, introduce an office implementation system, package for a one-month supply with a unit dose. Encourage enrollment in the Accutane survey, and provide educational materials to all of the stakeholders.

Here's how we changed the label in May of 2000. Two pregnancy tests, but no confusion, at specific times. No prescription until confirmation of the negative result from the second pregnancy test, and then, in a conversation with the pharmacist rather than written prescription. No woman should have a written prescription for Accutane.

Two safe, effective forms of contraception, and we will talk about one is primary and one is secondary. Primary, as you can see on the left, is either sterility or a hormonal contraceptive; the secondary, primarily barrier methods. Reinforce the one-month prescription only. We will supply a box to the pharmacist that has all the warnings that you've previously seen on our blister pack

but will be contained one month in one box, and there will be individual packets for patients to take their medication. I regret that I didn't flip this over, and you see the same formats on the back of each packet.

Reinforce the monthly pregnancy test and monthly contraceptive counseling. We will supply a progress note for doctors that on the top part is a simple checkoff list. Have I done or has my staff done every one of the things that is required. And since patients tell us that they often change contraception within the month and do not inform their prescribers, every month the prescriber has an opportunity to ask about that contraception.

There is a lot to do. So what we've done is we've created an office implementation system. Once you are considering giving Accutane therapy, you move into the 10-step method of the pregnancy prevention program, which I'll explain in a moment. If you are sexually active without contraception, you need to go for that contraceptive counseling. If the patient is sexually active with contraception and the prescriber feels comfortable, they can either be counseled by the prescriber or they can go to the contraceptive counselor. We would encourage everyone to see that contraceptive counseling.

Then there is the first pregnancy test which establishes you're not pregnant at the time of your office

visit. Obviously, if it's positive, no prescription for Accutane should be given. If at the second occasion the second pregnancy test is positive, obviously there is no prescription for Accutane given, but we would encourage people, because they're rather committed to doing this, to be sent then to the contraceptive counseling. No patient should receive our script for Accutane, no woman should receive a written one and no one should receive any Accutane until they are proved to be not pregnant with two pregnancy tests.

Once Accutane is prescribed, the patient will have two opportunities, once at the doctor, and once at the pharmacist within the unit dosing to join the Slone Epidemiology Unit, and then every month patients will come to their doctor, especially female patients will come to their doctor, for their 30-day supply.

This is what the schema looks like, and since it's confusing, we want to implement a 10-step office implementation system. It starts with the qualification checklist, which requires that a patient have severe nodular acne.

The next step builds on that information that they received in their qualification checklist as to information about the risks and benefits of Accutane.

Step 3 is a self-evaluation form, 10 questions

to assess whether a woman believes she can comply with this information.

Step 4 is a contraceptive counseling referral program, which used to be limited to obstetricians and gynecologists, but now will be broadened to include any licensed reproductive health professional. Some of our patients told us that they would prefer to go to Planned Parenthood, or that they would like to seek the advice of a nurse practitioner. So, we will support any option of a licensed reproductive health professional.

A question was asked about the informed consent. We do not get to the informed consent until the patient has been informed through the first four methods. The information consent form is in the form of 15 questions. Every question brings a patient, who initials at every statement throughout, all the knowledge that you need to have for Accutane, and to protect yourself, including the primary and secondary contraception choices.

The Accutane patient survey will be presented by the prescriber. The patient will join or not join as she feels is appropriate. What we have done is we have tried to help prescribers understand that all women need to join, even those women who believe themselves to be not at risk. All women need to join.

We also have a Be Prepared, Be Protected video.

It's brand-new. It's part of the label. It is a video that I'll explain later.

Of course, the Preventing Pregnancy: A Guide to Contraception, which is a very explicit booklet. We'll talk about that later.

The contraceptive knowledge test, which acknowledges does this person have the behavioral characteristics and the knowledge in order to avoid pregnancy.

And an Accutane information line and confidential contraceptive counseling line. Women can call this line 24 hours a day, 7 days a week, for reinforcement of the messages that their prescriber has given them.

Some of these steps help in selecting appropriate patients. And some of these steps help in educating patients. We are providing for subscribers a guide to best practices which has contraception education, the critical assessment and intervention skills, and how to start, initiate, and have a conversation about a very intimate topic. Also it explains the methods, all the support materials so that they can be used appropriately.

For patients we've changed the folder to Be Smart, Be Safe, Be Sure. It provides, as I've said before, step by step, encouraging knowledge, confirming the knowledge, all the way down to the contraceptive knowledge

test, which the patient really should be able to take and complete adequately.

We've also provided urine pregnancy tests, and we provided a sticker for the side. You can see it in your brown packages there. A patient information that has both the written instructions and the instructions in picture form for those people who may have difficulty reading or English is not their primary language.

I'd like to just tell you that these pregnancy tests are monoclonal and polyclonal antibody testing. They are twice the sensitivity that's recommended in the label, extremely easy to perform, easy to evaluate, standardized against the WHO international reference, and are 99 percent accurate on the 11th day post-conception.

For the women who had reported their following reasons, we have the videotape. The videotape is completely non-branded so that the patient can see it over and over again. Actually I would encourage them to lend it to their friends. There are five women who say these are the difficulties I'm having with contraception, and a counselor to help those people understand what they might have chosen instead of becoming pregnant.

Inside the Be Smart, Be Safe, there is a booklet on preventing pregnancy that talks about the patient's responsibility, what the patient must do because

the prescriber and the sponsor have done what we believe is appropriate and now we want to make sure the patients understand. We have line drawings of birth defects, discussions about avoiding pregnancy, the myths, the methods, the failure rates, and information about the contraceptive counseling line. As you can see, we have changed the line drawings to reflect damage that may be done to the child if exposed to Accutane in utero.

We have several educational initiatives. Again, I mentioned the Guide to Best Practices, which serves as a database to register prescribers for continuing medical education. The Roche representatives will be making office calls to implement the office implementation system. We will continue our dermatology residency program. We intend to have peer reviewed journal articles, and a web site for CME on this subject.

We have initiated a contraceptive counseling certificate program for registered nurses, which gives a certificate in counseling to nurses, LPN's, and medical assistants. The Dermatology Nurses Association is providing the CEUs, and it will be presented regionally and in state chapters.

For pharmacy education, we will distribute the professional materials to the pharmacy groups, individual pharmacists, and pharmaceutical associations. The CEU

articles will appear in their specific journals.

Here's a chronology of our actions so far. In March of 2000, we introduced the targeted PPP at the American Academy of Dermatology and at the DNA meeting. We received a lot of feedback on what we were doing, how we were doing it, and would it work, or would it be acceptable in their office. In April, we distributed the urine pregnancy test because we knew that would immediately address 26 percent of the pregnancies that we were observing.

In May, the FDA approved the label changes that we spoke about earlier.

In June, we distributed the first Dear Doctor letter and the contraceptive videos which were called for in the label.

In July, we have already started going to individual prescribers and doing office staff training.

In October, we will launch the educational materials which address the assessment and intervention skills, targeting the women on contraception knowledge and behavior, and providing that office implementation system.

So, how are we going to achieve our goals, and how quickly are we going to do it?

For prescribers, we will be notifying this month that a targeted program is available. Our

professional representatives will call on 90 percent of prescribing dermatologists by the month of January, and the remaining prescribers by March of 2000.

CME credit programs for dermatologists, which are our primary prescriber, but primary care prescribers, reproductive health prescribers and pediatricians will actually continue and will be competed by June of 2001. Every physician who writes a prescription for Accutane is immediately contacted and sent all our materials and then they are invited to call one of the medical directors to discuss the program. I know that I get those calls so I know they're getting the materials.

The dermatology resident education program will continue, and we expect to complete the resident education by December of 2002.

As far as the office staff metric, there are 35 chapters of the DNA. Twenty of them will be done by March of 2001, the rest of the members by September. In fact, last Saturday I gave the first certificate program up in Massachusetts. It was very well received. We got lots of feedback, and I'm happy to say that they learned a lot. We did a pretest, and they don't know about contraception either.

For the pharmacists, we are distributing the materials in October when we do the other targeted

education, and publication of a CEU article scheduled for March of 2001.

Dr. Mitchell went over this pretty clearly, but in having prescribers instruct their patients to join the survey, the number one reason patients tell us they don't join the survey is because they didn't know about it. So that changes that paradigm. We also will ask prescribers to send to Dr. Mitchell the survey enrollment forms. Dr. Mitchell and Roche have agreed that frequent feedback to patients and to prescribers is necessary, encouraging them to join the survey and encouraging doctors to realize that these pregnancies are still occurring. We will increase the visibility of the survey through all our patient education, and every promotional activity for Accutane will mention the Accutane survey. We will increase the compensation, as Dr. Mitchell indicated.

We intend to substantially increase the DAT arm, and to modify the questions to enhance the utility of the survey.

At the Roche call center, we receive 10,000 calls annually from health care providers, patients and family members. Over 1,000 of them are in reference to pregnancy and teratogenic potential. Not to report pregnancy, but to tell us, I'm not understanding this. We refer them to their prescribers, but we have registered

nurses who are now able to discuss pregnancy prevention with them immediately. We're developing a database of this so that we can help to understand what should be said to the patient and when that patient should receive the information.

Well, with all of this, it goes so far. But what we really need is to know why that small amount of women who become pregnant is different from the women who avoid pregnancy. So, we will begin some behavioral research which concentrates on the specific knowledge of the individual patient, what her attitudes and beliefs are, and actually having all that knowledge, what's her intention. A discriminant behavioral study will start in March of 2001. The participants will be prescribers, female Accutane patients, those who got pregnant as well as those who didn't. We will avail ourselves of the information of the women's behaviors who did not pregnant. The outcome should be to identify a risk factor for pregnancy.

If we go back to the risk management model and we create an Accutane risk management, we identify the issues and we put them into context. Pregnancy prevention is the issue. We have women who continue to become pregnant, but this drug is so uniquely efficacious that we want to be able to maintain this drug on the market. We'd

like to educate and select appropriate patients, and we have selected a strategy that is the promotion of risk-free behavior.

When implementing this strategy, we're going to use the targeted pregnancy prevention program that I've just gone through. Of course, it's necessary to evaluate results, and we'll do that, both through the Accutane survey and through the discriminant study. But in all of this, the most important is what happens to the patient. So, central to this will be patients, dermatologists, nurses, nursing assistants, and reproductive health professionals.

In summary, the 1988 pregnancy prevention program worked, and it worked for the majority of Accutane patients. A targeted pregnancy prevention program will ensure selection of the appropriate patients and address the educational needs of women who continue to be at risk. We will increase the enrollment in the Accutane survey to enhance the validity of the data. We will continue research to identify risk factors for pregnancy. In all of this, what we really want to do is avoid pregnancy.

Dr. Ellison.

DR. ELLISON: I will close our presentation with a brief review of other possible risk management options, and indeed I will be looking at the options

presented in the briefing document by FDA, which I think were very nicely summarized in that document and are going to be presented in a somewhat different way later today by Dr. Vega. I hope this suffices.

First of all, just to summarize again, as we know, Accutane use is increasing. We believe the pregnancy rate is declining, and that the pregnancy rate in women on Accutane is about 80 to 90 percent less than those with normal contraceptive use, as I think Dr. Mitchell demonstrated in the survey. For every 1,000 women treated with Accutane, pregnancy hasn't occurred in 997.

Really, that last statement does frame the dimensions of the problem, but also is the challenge. It's not a question of trying to change the behavior of 500 women and trying to make difference there. We're trying to make a difference in this smaller proportion of women and their behaviors because the absolute goal is the prevention of pregnancy.

As I opened the talk, we believe that the individuals' risk of pregnancy is decreasing. It's a total public health burden that is not in the absolute number of pregnancies. Exposed pregnancies have not decreased and needs to go down.

Now, to prevent pregnancy with this drug, every woman has to avoid pregnancy every day of therapy. Not

just the day they're at the physician, analogous to getting a liver function test or a blood test. Not just the day they go to the pharmacist to get the drug, which may be analogous to show evidence of something. They have to do it all the days in between. They have to have the tools. They have to have the motivation. They have to have the knowledge, and they have to have the support and the assistance. That really is the crux of this issue.

We're very pleased to be here with you today to discuss how we can help these women do this every day of therapy. As Eileen mentioned, we don't believe women who become pregnant on Accutane become pregnant intentionally. That, I think, is our challenge and that's our opportunity.

A first trimester teratogen such as this does require these two very difficult things: absolutely that someone is not pregnant at the start of treatment and won't become pregnant during treatment. Later trimester teratogens, of which this is one as well, also requires that the physician avoids prescription, knowing that the patient is pregnant. But the first paragraph is certainly the hard part.

I'd like to look at the options in the briefing document that FDA provided because that's what I had to work with, really. I thought they were rather nicely explained. So, I'd like to take options two, three and

four. Let me explain here, it is my understanding that the targeted pregnancy prevention program that you've just seen, plus these additional elements. Option two, three and four discuss no dispensing unless a pharmacist confirms a documented negative pregnancy test. I'm sorry, it shouldn't be pregnancy prevention. Option three would be this in addition to confirming that there has been appropriate patient compliance with contraceptive practice, drug sharing, blood donation guidelines. Option four is to train, register, and authorize pharmacies to dispense Accutane based on their ability to do the following options. This is my understanding of it. And all this would be in addition to the targeted pregnancy prevention program.

Let me look at this in a general sense. I'll discuss later why I think I can only discuss this in a general sense.

So, understanding that every woman must avoid pregnancy every day, a mandatory program tries to obtain compliance through conditional access to the drug. That's the nature of mandatory. That's the tool we have in mandatory programs. They in themselves do not achieve active participation through motivation and knowledge.

Now, in addition, adding them to programs that attempt to achieve participation through motivation and

knowledge is an interesting point, and the behavioral effects of this and the effects on motivation are somewhat unknown. It has been said actually in management literature that conditional programs and mandatory programs tend to disempower the motivation of people trying to do it on their own, but we have no evidence that this would occur, but we have no evidence that it would not.

Secondly, and I think this is of equal importance. They require a single channel of distribution and access to the drug. I think when Accutane was first put on the market, the alternate channel that we were most concerned about was drug-sharing. Indeed, we had reports of that. In at least the reports that we've had, this has come down as a percent. It still exists.

But the most important channel facing us now and going forward in the future is offshore Internet supply, which does not require a physician consultation, visit, or any of the information and discussion that goes with the targeted pregnancy prevention program. The ease of this is impressive.

We have identified three confirmed offshore sites that do this. We've notified FDA. FDA has indeed contacted one, but that particular site continues to operate. We're currently researching another six to confirm if indeed this works. There have been two small

seizures, obviously, for personal use of Accutane by Customs at the border in the last couple of years. We're not sure what that means in terms of overall use. Certainly this is something to consider in a program asking for conditional access to a drug, as we have more than one channel available.

The other issue is -- and I think these are important, although somewhat less important -- what a mandatory program would do as implemented in the pharmacy is stressing the completeness of documentation of compliance. Again, in the context of every woman having to avoid pregnancy every day, essentially the documentation would discuss, did you agree to be compliant, and were you compliant? Perhaps those two questions one month apart. In the 30 days in between the patient still must avoid pregnancy every day.

This would occur normally still in pharmacy practice in public at a pharmacy counter. Again, as I said, this does not deal with the effectiveness of a woman's practice of contraception.

Finally, in order for these things to be manageable -- and I think you can see the complexity of trying to build an optimal contraception and pregnancy avoidance program for a patient -- for these things to be possible and implemented on a large scale, you must enforce

a population standard for all patients, not necessarily an optimal program for the individual.

There is another issue here that we noticed, and I'll just read it to you in a formal sense. "Through the manufacturer, to be implemented by the pharmacist, we would be requiring additional qualifications or conditions from the prescriber, mainly documentation of certain things, that he has done certain things, or he is a certain qualified practitioner, to be fulfilled for the dispensing of a drug that are required beyond the state's licensure of that prescriber, or the state medical board's other regulations." We have not much idea of what this will actually mean in practice.

I think what it does say is, this is very much outside standard pharmacy practice. It doesn't meant it's impossible, it doesn't mean it shouldn't be done. We should understand that what we're asking is very much outside standard pharmacy practice.

Indeed, the pharmacist is now being asked to some extent to control the behavior of the doctor and the patient. I think we need to ask ourselves, is this appropriate and is this feasible.

An analogy here, one of the most important cognitive services that pharmacy offers patients and physicians is that when they see an inappropriate

prescription against the label -- that is to say, the dose might be wrong, as is usually within their competence to see, or indeed they may know of a drug interaction that the physician didn't know about -- it is incumbent upon them -- and it is one of the best benefits that they provide -- to call that physician and resolve the patient and achieve better patient care. If one asks them to refuse to dispense, that is now outside the standard practice of pharmacy and an interesting approach.

Secondly, the systems available to pharmacy -- and we do a lot of pharmacy programs in Roche that are quite extensive -- have issues with respect to how are you going to make it possible for them to do it on a large scale, how are you going to monitor whether they've done it or not, or how well they've done it.

And finally, with respect to registration of pharmacies and so on, and authorization to dispense, in terms of managing pharmacy compliance, should this professional cadre we've put in the critical path of pregnancy prevention -- there are a lot of issues how to do that.

Again, I don't think it's impossible. I think the issue is that these things have to be thought through carefully.

Let's just take very briefly this and then I

can close. I'd like to deal separately with the idea of mandatory registration of all female patients and the external data sources monitoring program impact.

On the second point, we fully agree with this idea. Indeed, we have been trying -- and you've seen the presentation very briefly of something we found in UHC -- to look for large external bases to see if we have some idea if it we're reasonably right or badly wrong with respect to the Slone pregnancy rate.

We're also very interested in collaborating with organizations like the OITS. California has referred that they get perhaps 40 calls in a year, and Connecticut has published 10. It's not the numbers that are important in this instance. It's the quality and depth of the calls that they get in terms of generating hypotheses of people who might be escaping the system that we can test in the larger databases.

But I want to come to the idea of mandatory registration. Frankly, we feel very strongly about this. Again, every woman must avoid pregnancy every day. Mandatory registration does not reduce the individual risk of pregnancy. We are asking something as a condition for prescription that does not reduce that individual's risk.

The only benefit -- and I'll come to this -- is actually a denominator of 100 percent of the user

population. Assuming one can implement that.

It could be argued that this is coercive, that the condition of getting a drug is a public registry versus private consent. That is, a woman who has SRNA, who clearly will not become pregnant, but does not wish to share information about her current or future sexual practice, contraceptive behavior, or pregnancy outcome with a third party, would be denied treatment. Versus a woman who refuses to sign informed consent, which is clearly based on her agreement to protect herself from individual risk is a very reasonable condition of access to drug.

Finally, our most serious concern is that there is a considerable risk of poor follow-up. You may recall the follow-up from the Slone was very good. Reliability of that response -- that is to say, with respect to truthfulness, especially if the denominator is full of people who would otherwise not wish to participate but did so in order to get the drug. And therefore, the chance of erroneously low pregnancy and compliance rates.

The danger here is that if, indeed, you make the follow-up mandatory or try to do that, you end up with a very large denominator and a much lower response rate. Then one is sitting here asking ourselves, with a response rate of 50 percent, do we worry about the 50 percent who didn't respond, and of that response rate, the unknown

number of people who may not be telling us the truth because this was the only way they could get to the drug. All of these are theoretical concerns, but they are real in the sense of it can certainly happen. What they are is unquantifiable at the moment.

We believe that clearly there is a risk, and I think the agency has mentioned this, that a common feature of all four options is the risk that the excessive burden on physicians and patients with no perceived individual benefit. This is control of compliance through documentary control, checking whether people did something rather than promoting them to do it. This could produce an indiscriminate barrier to access. That is to say, people who would otherwise qualify for the drug with the indication, be at risk of lifelong scarring and disfigurement and would clearly not become pregnant, would not be able to get the drug.

Now, what experience we have? As I said, I wanted to return to this about the theoretical argument. What experience do we have in terms of looking at these kinds of programs in the prevention of pregnancy, which is different than liver function tests, CBC's and so on?

Indeed, we have the Accutane pregnancy prevention program, which is a voluntary program, initiated in 1989. I want to point out that it's 200,000 women

treated per year now. They are basically young, healthy patients. It's a well-known unique drug, and there are alternate channels available. It has been evaluated, published, and publicly reviewed.

I've given you in your handout two tables, which I'm not going through now, where we tried to organize the targeted PPP against some of the issues brought up in the questions today.

We also have experience with the STEPS program, as mentioned. It is a mandatory program. The basic design is basically known, but it has not been published. There was a recent presentation, actually, in Wales this weekend. It has not been publicly reviewed, so what we know about it in Roche is somewhat indirect. We believe that there is a small population involved which we manage to see in IMS, that the majority are ill, older women, that greater than half of them have malignancies, and we're not sure if there are alternate channels for access.

Basically we think it's a very good experiment, or test, if you will. It's also very important for the people taking this drug. The problem is that it hasn't quite reported out yet. And many of the elements that are being discussed here are not tested in STEPS either. We have not been able to see testing of some of these elements or any experience with them in our search, so actually our

comments on this have to be taken as where we would identify possible risks against possible benefits.

Finally, based on what we know versus the projections and extrapolations, and balancing the likelihood of success, the risk of compromising current success, and the risk of denying treatment to patients who would not otherwise become pregnant and would qualify for treatment, we think that to prevent pregnancy in women prescribed Accutane, mandatory programs that we are discussing here are still untested, and that they have unknown benefits over the TPPP, and unquantifiable risks which will be difficult to ascertain and reverse. This is not to say that some of the functionality that is being tried to achieve is not a good thing necessarily, but we're concerned about the mandatory aspect.

Given that every woman must avoid pregnancy every day, we believe the TPPP becomes a shared responsibility of Roche, prescriber, pharmacist, nurse, reproductive health professional, and most importantly, the patient. We believe the TPPP is the best method that we know at present to assure active participation of all parties to prevent pregnancy and has the optimal chance of success, based on what we know, with the least risk.

We're committed to the absolute goal of pregnancy prevention, and the continual improvement of the

targeted pregnancy prevention program. Thank you for your attention.

DR. BERGFELD: Thank you, Dr. Ellison, and the Roche professionals that presented this morning.

We could field a couple of clarifying questions before we dismiss for lunch. Are there any? Yes, please.

DR. BRANCH: I was surprised that, given that you have another number of interventions that are in the Slone program, and you have an outcome in terms of pregnancy, that you didn't provide an analysis of relating the interventions that you've actually measured to the outcome to see if there is any evidence that as you comply in the reporting of one, two, three, four of your steps, is there actually an improvement in your outcome. Is there any relationship to the outcome from whether you've signed the consent form, whether you've gone through step A, B, C, D, to the actual pregnancy rate?

DR. ELLISON: Let me just clarify this, and then perhaps Allen would like to comment. Basically we're saying that the data sources we've shown you are what happens in the wholesale population, the DAT arm and the AT arm, irrespective of whether people became pregnant. And then what Eileen Leach was talking about is the people who became pregnant, what can learn about them. We believe those are the behaviors we need to target.

The question is, can we link those people and those data to the larger data. Is that what you are referring to?

DR. BRANCH: That's what I'm referring to. Do you have evidence that as people comply with the first phase of your program, did it actually confer benefit in terms of a lower pregnancy rate?

DR. MITCHELL: I can't answer the question the way you've asked it. But what we have done is an analysis that's pretty comparable to what Eileen Leach presented, which is that there are no glaring behavioral missteps that identify the women who became pregnant in this survey, that many of them, the large majority of them knew the risks, knew they weren't supposed to get pregnant. As you'll notice from the information we've presented, the large majority of women got pregnant as a result of presumed contraceptive failure. This gets to the issue of contraceptive failure as a phenomenon that can be reduced but not eliminated.

DR. BRANCH: You actually had quite a number of people who were taking two contraceptives, for example. You showed one graph that was a certain age, and a lot of people have taken note of your advice. If you just analyze that group, do any of them get pregnant? Are you able to show that when people follow your advice, that you actually

reduce the pregnancy rate?

You asked the question right early on, what rate you should be looking for, what would be a sign of success. Have you looked in your own data to see what is the most successful strategy?

DR. MITCHELL: As you could guess, with a rate that is as low as we have, it's very hard to get stable estimates. What we've been able to do is to look at contraceptive method, which sometimes is accompanied by two or more, sometimes not, and been able to see differences according to method, but I don't have the specific analysis you're describing.

DR. BERGFELD: Dr. Holmboe.

DR. HOLMBOE: Eric Holmboe from Yale University.

You had mentioned that a lot of this is going to ultimately depend on the patient to carry out and be compliant, and I'm glad to see that you're going to look at some of the behavioral research to see if there are certain things that predict attitudes.

One piece I see that's missing, though, that was brought up earlier is the whole issue of the process between the patient and physician because ultimately you've kind of reached a plateau, and that's really the next area that's probably going to be necessary to see further

reduction. In fact, most people now would discard the term "informed consent" and look it more as informed patient decision making, which involves a lot of different aspects.

Do you have any plans to look at that process and see how you can facilitate that process?

DR. ELLISON: I'd like to introduce Eileen Leach to discuss that a bit in terms of what our program is, but I'd just like to preface our remarks.

Actually the TPPP is based upon what we know. Things like getting to the level of attitudinal and cultural, and behavioral research is going to give us the next link, to figure out precisely what are those motivating issues and how can you recognize them as a physician, and turn that around into the next round of physician education. Eileen will talk about what we're doing right now around those issues.

MS. LEACH: The office implementation system has to be drawn from how things are done and when things should follow the other. The packet that patients were given originally had 10 pieces of paper, and which one do you do first. So from the feedback that we got, we wanted to make sure that patients had the qualification checklist first, because that has the 10 questions about whether you actually qualify to take this drug.

The next would be the information in the packet

on Accutane itself, with all the pregnancy warnings. So, once you know that you qualify and you have the information, can you pass the self-evaluation quiz?

Following that, do I need contraceptive counseling? That's what the self-quiz tells you. Then you have the opportunity to go for that counseling.

Everyone, as you can see, has a number on them.

Only then, when you know the risks and the benefits, you know what the purpose of all of the contraceptive counseling will be, and you elect to take adequate, two forms of safe, effective contraception, do you get to sign a consent form. Now we are in a situation where the woman is fully informed and can make an informed consent.

After that the survey form is presented to her, she knows whether she wishes to join the survey or not.

The seventh is watching the video which, as I said, will tell you about the most common reasons that people get pregnant.

Step 8 and 9 is about contraception itself, take it home, learn about the myths, learn about the things that you believe are true which are not, and then take a contraceptive test. Make sure you know what you think you know.

Then step 10 is reinforce your information by

calling up on the telephone.

I see you have another question.

DR. HOLMBOE: I would just make the observation that simply giving patients a packet does not necessarily mean they're going to be fully informed. Somebody is going to need to sit down with them. That's why, again, this whole process with the physician or somebody in the office I think is going to be very important. The risk communication literature tells us that although these things are very useful to patients, patients actually greatly value the information they get from the physician, and many times don't fully understand what's in the packet.

I think the informed consent form is very nice, but it's also very extensive, it's small print. What I find interesting about it is that there is no quantification of what the actual risk is should you get pregnant. In fact, it's missing in all the materials, something else you may want to consider.

The risk communication literature also points out that patients often want their information in different formats, not just qualitative data. So, I think there are some other things you need to think about there.

MS. LEACH: I understand. I think that we do have some information, as you review the material, in both the physician's guide and in the patient's guide to

contraception that tells them what the risk actually would be. It even includes line drawings about what it looks like.

DR. ELLISON: Dr. Holmboe, first of all I want to thank you for the comments because they are useful in terms of your perspective on this. There are a couple of things we hadn't really thought about, I think. But there are some things we did.

I just want to make sure you understand the qualification checklist is something the patient brings to the dialogue with the physician, to be reviewed in the informed consent. If we ask the physician to sit down and go through that with a patient, you know what will happen. On the other hand, if the dialogue between the physician and the patient includes that patient's self-evaluation once completed, it's then reinforced and put into context. So, it's to make that much more efficient so that actually that discussion about qualification will be done.

It's a little bit like -- well, I wouldn't want to put it in this context -- the waiting room form. I really don't want to put it in that context, but it's a homologue. Where people will fill things out. If this is used correctly, which it rarely is, that is then a subject for the physician to get right to some points that need to be covered.

The informed consent. We had a lot of discussion about whether or not we should put in the fetal malformation rate, the rate of risk of major malformations if you had a live birth. The work done by Dr. Lammer is excellent, but the confidence intervals are somewhat broad. I think there was a discussion back in the late 1980s between the agency and the company about the risk of putting that in. I think that can certainly be reopened.

DR. HOLMBOE: I certainly recognize the problems with the efficiencies needed by the physician. The average office it is oftentimes only 15 minutes. But we do know from research, some by Wendy Levinson and others in Chicago, that there is a lot of information that doesn't get transmitted. I think anything you can come up with that helps a physician do it efficiently to provide both qualitative and quantitative information that the patient can then take with them to make sure they understand it is going to be critical.

DR. BERGFELD: You need to shrink this response a little bit.

DR. ELLISON: So, basically -- and this is important thing -- if something is given to the patient by the physician to do, versus sort of handed out as a package, that's clearly better. What we try to do is to get the physician to review the response with the patient.

DR. BERGFELD: Dr. Rosenberg.

DR. ROSENBERG: Rosenberg, Tennessee.

I'd like to move a little bit beyond the prevention of pregnancy toward the prevention of birth defects. Some years ago, discussing this issue with a dermatology practitioner colleague, he said, you know, no matter how hard you try at contraception, there are always going to be some failures. He said, the way I do it, I sit down with the young woman and I say, look, if anything should happen and you should be come pregnant and deliver a child with a birth defect, and it happens, it's a disaster for the child, a tragedy for you. Nobody's life is ever going to be the same. It just can't be done. He says, I'm going to ask you two questions. He said, could you morally, ethically, intellectually, and emotionally face the prospect of having a pregnancy interrupted should it be found that you became pregnant while taking this drug? Or could you absolutely commit to sexual abstinence for just 20 weeks? He said, if they don't sound enthusiastic about either of those, he said, I won't write the prescription.

I'm not suggesting that this is necessarily where we ought to be going, and I understand perfectly that talk of pregnancy interruption, abortion, or choice or whatever is perhaps a third rail for international corporations, but this is such an important subject that I

would feel remiss if I didn't bring it up. I must say that's the way I've practiced over the years.

DR. BERGFELD: Thank you. Dr. Abel, and then Dr. Epps.

DR. ABEL: The point was made previously that knowledge doesn't always transmit into behavior, and I am particularly concerned about one group. I know the greatest pregnancy rate was due to contraceptive failure in 66 percent, but 23 percent of women had no contraceptive use. Then going back to the pregnancy risk categories, of the 57 percent that were not sexually active, 56 of those 57 percent were not using birth control.

I'm concerned about the need perhaps for some special counseling among those who are not sexually active, being that their situation might change. It's difficult sometimes to convey the risk in a patient who thinks that this is a very hypothetical situation, and that's not going to affect them because they are in this sexually inactive group. So, I think there is a need for special counseling in that group, and what can be done to address this. Maybe the behavioral research will turn up something.

DR. BERGFELD: Thank you.

Dr. Epps?

DR. EPPS: Just a couple of issues. I guess Dr. LaFlore cited some data from the U.S. National Health

and Nutrition Examination survey. There have been subsequent surveys since 1972, 1974. Do you have any of the data that would support not only an increase in the acne, whether it be prevalence of nodular cystic acne, to support the increase in the prescriptions given? Is it part of the baby boom, or the baby boom echo, or is there really that much more nodular cystic acne?

DR. ELLISON: First of all, as far as a community-based survey with the rigor of NHANES that was done in 1974, where dermatologists against a rigorous protocol evaluated thousands of people, such a survey has not been conducted since in the United States, as far as I know, with respect to dermatology, and we certainly have been looking. NHANES has been conducted since, that's for sure.

The great tragedy for dermatology is, for not only acne but other diseases, is that actually very well-done piece of work, was not repeated in subsequent years. I'm sad to report that it's not going to be done to that rigor in 2000 either. So, we are sort of stuck with the prevalence data from 1974, which is the pre-Accutane era.

Having said that, the work was rather well done, and Dr. Lammer referred to various discussions in previous advisory committees about a decade ago.

Dr. Stern went back to the original data tapes

of NHANES and found that you could actually look at inflamed nodular acne and count them better than just the categories of grade 1, 2, 3, 4. So, we're able to look at a revised prevalence rate, which he has in fact published in 1992 from that survey.

Now even so, we think that prevalence simply provides a kind of quantitative context even though it's certainly larger than the current prescriptions of Accutane. We think Accutane is certainly not pure prevalence, and calculating an incidence rate is extremely difficult because duration varies very widely. Relapse rates have been reported to be from 3 to 39 percent, and both of those will vary from age and gender, as does prevalence. So, we are stuck with it as a quantitative context, and it certainly is larger, even when you project it to 1998 population terms, than the current use.

If you look at surveys of medical utilization, and also surveys of what physicians say they do, it is consistent that at least there's not a vast or large number or ever-increasing number of use in milder acne. This certainly occurs and we think it's probably somewhere between 10 and 15 percent, and it's just an estimate and a guess of prescriptions.

We could go over this in some degree of detail, but we found that it really is to try to provide a context

for that use. The reasons for use cannot be entirely numerically explained. There are quite a few that are in the appendix. I would put up one slide, Dr. Bergfeld, or do you want me to stop?

DR. BERGFELD: I'd prefer if you stop. We have time this afternoon to have you continue, and I hope that all of the committee members will keep their questions active in their mind or written down.

We're going to adjourn for one hour. We'll be reassembling at 2:15, and we'll start at 2:15. We'll then go through any briefing questions, the open public hearing, and then we'll get into some of the more discussive areas. So, we are adjourned until 2:15.

(Whereupon, at 1:15 p.m., the committee was recessed, to reconvene at 2:15 p.m., this same day.)

AFTERNOON SESSION

(2:15 p.m.)

DR. BERGFELD: If everyone will be seated, we'll begin with the afternoon session.

As you might recall, we are focused on the Accutane pregnancy prevention program. We have heard the FDA. We have heard the Roche presentation, and we are now going to move forward to the open public hearing.

I'd like to explain the rules of the road of the open public hearing, and that is that we have scheduled speakers. They have been allotted 4 to 7 minutes to present. They will be on a timer. The yellow light will go off, and when that happens, you are to quit. I will remind you. I would also like those presenting to state who they are, who they represent, and if there is any conflict of interest.

Our first speaker that I would like to bring to the podium is Donna Richmond, Vice President, Association of Reproductive Health Professionals here in Washington, D.C.

MS. RICHMOND: Good afternoon. My name is Donna Richmond and I'm Vice President of the Association of Reproductive Health Professionals here in Washington, D.C.

The Association of Reproductive Health Professionals is an inter-disciplinary association composed

of professionals who provide reproductive health services or education, conduct reproductive health research, or influence reproductive health policy. ARHP, founded in 1963, has a mission to educate health care professionals, public policy makers, and the public. The organization fosters research and advocacy to promote reproductive health.

ARHP, as a nonprofit, educational organization, firmly abides by national accreditation guidelines for industry support by producing credible and independent, enduring materials for clinicians and consumers. In 1999 we received funding in the form of an unrestricted educational grant from Roche Pharmaceuticals to develop and implement an educational and training program. Funding was not provided for participation in this review.

Education and intervention is the key to providers' helping patients make informed contraceptive choices and prevent mistimed or unwanted pregnancies. This is especially important in treating adolescents and young adults, who make up the majority of Accutane users.

The interaction with the dermatologist or other health care provider represents an important, salient teaching moment because young adults and adolescents are open to learning about reproductive issues. While a course of Accutane therapy lasts only a few months, the

information received on reproductive health could carry them through their entire lives.

This is a time of physical and emotional growth for young adults, who are particularly sensitive to issues of trust as it pertains to their privacy and confidentiality. If patients are forced to give mandatory documentation of very sensitive and personal issues, we run the risk of losing the opportunity to educate them, we run the risk of leading them to unconventional and potentially unsafe alternatives.

This is why Roche asked the ARHP to bring together leading experts in dermatology and reproductive health in order to update and to refine the PPP, which is targeted to preventing mistimed and unwanted pregnancies, as we have heard this morning. The program components are aimed at helping providers and patients become more comfortable with counseling and assisting patients with making informed choices. This is truer now than ever before because reproductive health is becoming part of all medical disciplines.

Thank you.

DR. BERGFELD: Thank you.

The next speaker is Dr. Barbara Reed, dermatologist, American Academy of Dermatology.

DR. REED: Good afternoon. My name is Barbara

Reed. I am a member of the board of directors of the American Academy of Dermatology, or the AAD.

The AAD is the largest, most influential and most representative of all dermatologic associations. We have over 11,000 members and we represent virtually all dermatologists in the United States, and we have a growing membership with international members as well. The academy is committed to the highest standards in patient care, education, and research in dermatology and related disciplines.

In addition to my responsibilities with the academy, I am an associate clinical professor at the University of Colorado Health Sciences Center in Denver, and I have a busy private practice.

As a dermatologist I have had a personal interest in the use of dermatologic drugs during pregnancy. I have written and spoken nationally on this topic, most recently last month at the AAD's meeting in Nashville. The subject of my talk was management and diagnoses of dermatoses during pregnancy, and we discussed how to clinically assess the risk, as well as how to help with clinical decisionmaking when deciding on use of a drug during pregnancy.

My interest in this has been long-standing and a little unique. I've been a dermatologist since 1984, but

prior to that I spent 12 years practicing office gynecology, primarily in the areas of birth control and pregnancy counseling. My knowledge of gynecology has proven very helpful to me as a dermatologist, since dermatologists do use a number of teratogens, including Accutane, or isotretinoin.

In 1948 Drs. Salzberger and Salderns gave the following description of acne. There is no single disease which causes more psychic trauma, more maladjustment between parents and children, more general insecurity and feelings of inferiority, and greater sums of psychic suffering than does acne.

And while acne is most related to the teenage population, this disease is not restricted to any age group. I have quite a number of patients in their 20s and 30s and 40s. In its most serious forms, acne can lead to severe scarring which is permanent. In cases of severe acne, we have a limited number of treatment modalities. We can use antibiotics, and for women we can sometimes use female hormones.

I prescribe isotretinoin, or Accutane, only after these other methods have failed, and educating patients as to the risk of pregnancy with this drug is always undertaken. It is education not mandatory registration that will be our most powerful tool in

pregnancy prevention.

Why not mandatory registration?

First, mandatory registration will, by design, restrict the number of physicians and pharmacists that can provide Accutane. Now, during the time that I'm treating a patient for acne, a relationship develops, and in the context of this relationship, we have a discussion on pregnancy prevention. At this crucial juncture, if you force my patient to change from a person who is not registered to one who is, you are going to severely disrupt the physician-patient relationship. So, my patient will have this intensely personal conversation with a complete stranger, and the likelihood that this stranger is going to be on her health care plan and in a place close her decreases in direct proportion to the size of the city, so that in a rural community she may have to travel many miles to get care. Even in cities, locating a registered pharmacy will be a challenge.

Second, if the concept is to prevent drug-induced birth defects, which we call developmental toxicity now, because it's not only the structural things, as we've heard, but learning abilities and behavioral characteristics, if that is the concept, it's a very far-reaching concept.

Non-steroidal anti-inflammatory drugs are

teratogens. Used in the last half of pregnancy, they can close a large blood vessel that needs to stay open until birth. That's the ductus arteriosis. The ductus arteriosus closure can lead to congestive heart failure and can also leead to failure of the kidneys to develop. These drugs are available over the counter. We don't know how many women gave birth to babies with this problem.

Secondly, and I realize this is not under the purview of the FDA, but let's talk about alcohol and fetal alcohol syndrome. Fetal alcohol syndrome causes low-set ears, nervous system abnormalities, tiny brains, mental retardation, and attention deficit disorder with hyperactivity. Last year over 12,000 women gave birth to babies with fetal alcohol syndrome. Are we going to have to have a registry for buyers and sellers of non-steroidal anti-inflammatory drugs and alcohol? Cigarettes is another one.

Finally, it is impossible to legislate pregnancy prevention. The issue of pregnancy is complex. I've had patients who got pregnant despite being in impossibly difficult circumstances, and stated simply, some of it was birth control failure, but a lot of it was just risk-taking, similar to driving too fast or flying too high. But this form of risk-taking can compromise the lives of three people.

Restricting Accutane use will have the unwanted consequence of driving unauthorized use, such as through the Internet.

We must facilitate in our patients a strong commitment not to become pregnant, but no authoritarian program will ever control pregnancy. To the extent possible, pregnancy prevention will happen through education.

We feel that the response of industry to this drug and its problems has been outstanding, and I have no conflict. The American Academy of Dermatology is solidly behind education and re-education of both physicians and patients, both male and female, about the risk of use of Accutane during a woman's childbearing years. We are committed to pursue and increase our effort in this regard to further decrease the incidence of pregnancy with the use of Accutane.

Accutane is a very, very valuable drug for the treatment of severe acne, but it is education, not regulation, that is the key to safe use of this drug.

Thank you.

DR. BERGFELD: Thank you.

Would you like to ask a question? Could you identify yourself, please?

MS. GLORIA ANDERSON: Yes. Gloria Anderson.

Have you conducted any studies related to this drug?

DR. REED: I personally have conducted no studies related to this drug.

MS. ANDERSON: Are you sponsored by anyone?

DR. REED: No, I am not.

MS. ANDERSON: Thank you.

DR. BERGFELD: Thank you.

Then moving on to our third speaker, Dr. John Strauss, Professor Emeritus, Department of Dermatology, University of Iowa, and former President of the American Academy of Dermatology.

DR. STRAUSS: Madam Chair, members and guests in the room, you've already been told that I am a former President of the Academy and currently am Professor Emeritus at the University of Iowa. I was head of the Department of Dermatology for 20 years, and since taking my emeritus status last February, I have been a consultant on a part-time basis with Roche labs. However, I am making this statement not as a representative of Roche, but as a practicing dermatologist, as I still maintain a referral acne practice.

I also add that my professional life in dermatology has been devoted to improving the treatment of acne. I have just short of a half century of experience.

I was one of the original investigators with Accutane, having started with it in 1978. I'm even a veteran of some of these meetings in the past, as Dr. Lammer pointed out.

I appear today before you as a strong advocate for those patients with severe resistant acne. For them Accutane is often a miracle drug. I could show you innumerable before and after pictures, all of which will show you the same thing. But I just want to show you one case today.

This is a young woman that I saw in consultation about having treatment with acne. Look at her face. What she has is devastating, as you can readily understand. Her treatment before I saw her was extensive and included just about everything that had been given for acne. In fact, her life was miserable at this point.

This is a slide that she sent me subsequently, and if you can't read this, it says, "Thank you, Dr. Strauss and Dr. Schultz." Dr. Schultz being the resident who saw her with me. This to me is a dramatic improvement.

I just show you one more photograph, which is also an after-photograph, taken after two courses of Accutane.

This patient is definitely what I call an acne success. Personally I'm probably as proud of this set of photographs as any patient care photographs that I have

ever taken or reviewed.

There is no need for me to show any other examples. We are discussing a drug that is unique and is essential in the care of a segment of the acne population of patients with acne. I will admit that this patient represents the far end of the scale in terms of severity, but for many patients like her, the results you have seen are remarkable and can salvage an otherwise miserable existence.

Results like this are easily documented, and when I personally talk about acne to audiences, I focus not on the proven efficacy of the drug but on the unwanted effects, and how to prevent them or control them. I think that all dermatologists should continue to be updated on the maintenance and safety when using this drug, and I feel that the manufacturer is doing this through frequent updates, particularly with the pregnancy prevention program and the changes in labeling, which I realize in some instances is FDA-mandated.

As an individual practitioner, it was my decision that this patient be treated with Accutane, and it should remain my decision and not that of the manufacturer or pharmacist or anyone else. This means that I as a specialist in the management of acne, as well as all individuals prescribing the drug, must be responsible for

its safe use. I am convinced that education of the physician and the patient is the way to accomplish this rather than registration. Education is where our efforts need to be continually updated and expanded. Anyone who uses this drug must know how the drug acts. Furthermore, the proper administration of Accutane involves a partnership between the physician and the patient and others, which is definitely being fostered by the continuing education programs.

Thank you for allowing me the time to present this statement.

DR. BERGFELD: Thank you, John.

We're going to move on then to our fourth presenter, Dr. Irving Katz, a dermatologist from Golden Valley, Minnesota.

DR. KATZ: Thank you, Dr. Bergfeld, members of the committee, and ladies and gentlemen. My name is Irving Katz. I'm a dermatologist from Minneapolis. I practice with 12 other dermatologists, and I primarily do clinical research.

I do have a number of conflicts of interest. Those conflicts of interest include the people from Roche because I've done a number of studies for them. But I want to tell you some personal things.

I have personally experienced the hurtful

consequences of severe acne, and I believe that Accutane is an effective drug and it can be used in a safe manner.

As a dermatologist, I treat people with this. Personally speaking, having had severe recalcitrant acne at a time when there was really no effective treatment, I can remember the trauma that I personally endured. Think of a young adult or a teenager with multiple red blemishes, some of which are the size of a pea or larger, huge red areas on the face that can take months to resolve, scars that can be permanent. This does little to enhance one's ego. Therefore, we've heard this morning about the psychologic consequences that can occur, and that indeed happens.

As I mentioned, I do clinical research, and in part my experience with acne determined my career field. That's how I got interested in dermatology. I have got scars on my face and tainted remembrances of that time in my life.

Recently our group had an opportunity to participate in a clinical trial with Accutane in 40 patients with nodular cystic acne. I would like to share with you some anecdotal impressions, not about the clearing of their face or the number of lesions that they have or the counts went down, but anecdotal impressions about the nuances of the patients' attitude and how they appeared to both myself and our staff.

Patients with severe acne come into the office a little different than other patients. Many times they don't make direct eye contact with you. Their eyes are directed toward the floor. They are somewhat muted. But following therapy with Accutane, one can see a remarkable change in their attitude. They are more animated, their eye contact is more normal, and one can see a remarkable change.

But hearing some of the things this morning about safety, safety is an extremely important thing. As a dermatologist, and speaking for other dermatologists, nobody wants to do any harm. I think by adhering to certain standard procedures that go on in our office, such as getting an informed consent prior to giving a drug like Accutane, both in an oral and a written fashion, having a team doing this, not just the physician, but having the nursing staff participate in this in a very active way, getting feedback from the patient, doing the pregnancy test, and having a monitoring system in place, one can go far to assure a minimal risk for pregnancy.

The dermatologists and other prescribers have to recognize the incidence and consequences. I found Dr. Lammer's presentation very enlightening, and Dr. Rosenberg's question was I think right on point. What can do you? There possibly may be some pregnancies that occur,

no matter what you do. One thing I thought of, you're giving away free pregnancy tests. Why not do the pregnancy test at home more frequently? Women don't want to have a malformed child. Given that and given the pregnancy test, and if you have compliant patients, why not do it once a week? What difference would it make? It's possible, maybe, to prevent some of the unwanted effects of an unintended pregnancy.

With that I'm going to close, but I would like to reiterate just a couple of things, that Accutane is an effective drug for recalcitrant nodular acne, and I think it can be used in a safe manner, with proper guidelines. I think the physician is the best person to direct that. In doing so, you can really change a person's life.

Thank you very much.

DR. BERGFELD: Thank you.

Our next presenter is Nancy Vargo, President of the Dermatology Nurses Association.

MS. VARGO: Hello. Good afternoon. Thank you for inviting me.

As you said, my name is Nancy Vargo, and I'm President of the Dermatology Nurses Association. I would like to disclose that my transportation and hotel expenses are funded and will be reimbursed by Roche, but I am not being paid for my statements today.

The Dermatology Nurses Association is nationwide. We have over 2,300 members. Our members are registered nurses, licensed practical nurses, and also associate members which are non-licensed personnel. We work as part of the health care team in our offices, along with our dermatologists and other providers, which include nurse practitioners and physician assistants.

The mission of the DNA is that we advance the practice of dermatology by providing quality education, fostering high standards, and promoting wellness. By far, education is the heart of the DNA and to the DNA members. As we educate each other, we share that knowledge with our patients so that they too can make informed decisions about their health care.

In preparation for this statement today, I conducted a survey among our membership and sent an e-mail out to 600 members asking them what is the protocol in their offices regarding Accutane and female patients. The response was brisk and I received back about 100 responses in time for this meeting.

I can tell you that they are, indeed, working as members of the health care team. They are providing the education to their patients, along with their dermatologists, regarding the normal side effects of Accutane, and female patients are receiving the pregnancy

counseling. They're working with the pregnancy checklist and they utilize the Roche materials. The respondents also had room for comments, and I could tell that they are very, very proud that they are part of the initiative to make sure that their patients are safe.

Someone asked about the process of educating patients and how it can be ongoing. And Dr. Katz said it so well, and that is that all across America in the offices of dermatologists are dermatology nurses, many of whom are DNA members. Education is what we do, and we should be and could be involved, if we're not already, in that process of educating the patient initially, monitoring their laboratory tests.

Personally I would like to see them have to come in monthly for their pregnancy test. You do it and then they get their prescriptions, and it gives you an opportunity once again every single month to give that key pregnancy prevention information that is so critical to the patients. Having them come in and talk directly with the nurse or with the physician emphasizes the absolute, utmost importance of preventing pregnancy.

So, the message I have for our members who are so proud of the job they're doing is that we're not doing enough. I don't know if you are aware, but the DNA members are very, very committed and dedicated to their patients.

If I were to give them a mission -- and I will -- and the mission is that we need to do more, then I know that they will do more.

First of all, on the nursing education part, Roche has kindly involved nursing and we are going to have the pregnancy prevention workshop at our next annual convention. But we are also organized on the local level and we have chapters all across America, and Roche is going to go to each of those chapters and educate the nurses and nursing assistants at the grassroots level of what needs to be done to keep our patients safe and to allow them to still continue to use unrestricted Accutane.

Our members believe that the effectiveness of Accutane justifies its use as long as it is carefully prescribed and closely monitored. We have heard testimonies already -- and I wish I could read some to you -- about the fact that every day in our offices we face the faces of patients with cystic acne. We know how devastating it can be and how it can lead to a lifetime problem with the disfiguring scarring that can result.

On a personal level, there was a teenager in our family many years ago who suffered from cystic acne, and I can tell you that it impacted his self-esteem. It lowered his sense of self-worth and confidence and inhibited his ability to establish relationships with his

peers and with others.

After trying many other modalities, Accutane was new at the time and his dermatologist placed him on Accutane. It was a miracle and a miracle in two ways, not only that it cured his acne, which never came back and prevented scaring, but the teenager came alive. He could look people in the eye. He can go about the business of growing up. It really is, indeed, a miracle drug.

In closing, I would like to try to emphasize -- and I don't know how to convey this -- the dedicated commitment that your nurses have to the safety and well-being of their patients. They will rise to the occasion. They're intelligent. They know what can happen with Accutane. They don't want it to happen. They will do whatever is necessary to make sure that that doesn't happen.

We now have new educational materials that will be coming from Roche. That is very exciting. Along with closer monitoring of the pregnancy results, I believe that we will make a difference, and as members of the health team along, of course, with the dermatologists at our helm, I believe that we will make a dent in this pregnancy problem with Accutane.

Thank you for your attention.

DR. BERGFELD: Thank you.

Our sixth presenter is Dee Quinn, President of OTIS, Arizona Teratology Information Program.

MS. QUINN: Thank you. My name is Dee Quinn. I'm a genetic counselor at the University of Arizona and also current President of OTIS.

OTIS is the Organization of Teratology Information Services. It's a nonprofit network of 19 member teratology information services, or TISs, 13 individual members, and 4 services in Canada. TISs provide comprehensive and multi-disciplinary resources for medical consultation regarding prenatal exposures.

OTIS is concerned about the number and persistence of exposed pregnant women and their developing babies to Accutane despite actions taken by the manufacturer to warn women about teratogenic risks. Aggregate data from 16 teratology information services identified an average of 14 Accutane exposed pregnant callers per year between the period of 1995 and 1999. As of August of this year, double that number, or 28 calls, were received from exposed pregnant women.

Of greatest concern are those exposures in which information about teratogenicity or access to pregnancy prevention methods have reportedly been inadequate. Of further concern are those women who have not enrolled in the Slone Epidemiology Unit's pregnancy

survey program nor have reported their pregnancies to the manufacturer or to the FDA.

OTIS is supportive of the current efforts by the manufacturer, Hoffmann-LaRoche, and the FDA to decrease the number of prenatally exposed women. Although OTIS members are aware that not all prenatal exposures can be prevented, we feel that our combined efforts could make a significant impact on the number of exposed pregnancies.

The importance of adherence to the current pregnancy prevention program cannot be overstated. An additional concern is the use of this medication by young women. One area in which the system appears to be breaking down is in the provision of effective contraception. Several studies in the late 1980s and early 1990s documented that approximately a third of reproductive age women using Accutane were not also practicing contraception despite having been told about teratogenic risks.

Given the inherent difficulties of discussing sexual activity, particularly in young women, one dermatologist in Utah approaches the issue in this way. He does not ask the patient if she is sexually active, but instead informs the patient that if she wishes him to prescribe Accutane for her, she must use an effective birth control method. He evaluates risk factors for the use of hormonal contraception with a tool developed by his local

Planned Parenthood. If no risk factors are identified, he prescribes hormonal contraception along with the Accutane.

Individuals with identified risk factors are referred back to the Planned Parenthood for further reproductive counseling. They are then required to return with documentation of this visit and only then will Accutane be prescribed.

The patient is also required to register with the Slone Epidemiology Unit before leaving his office. Availability of emergency contraception is also discussed in the event of unprotected intercourse.

The key elements of this strategy is the focused efforts on the part of the provider and the patient. Although this approach is not appropriate for all individuals, strategies that aim to prevent pregnancy during Accutane therapy will need to address the unique difficulties in ensuring effective contraception in women.

To further reduce pregnancy exposures to Accutane, OTIS would like to see stricter measures mandated to regulate the prescription, dispensation, and use of Accutane. A program similar to the STEPS program for thalidomide would be beneficial.

Through its membership, OTIS has the ability to provide counseling to patients and assist in monitoring and investigating reported fetal exposures. By combining our

efforts, we feel that we could make a significant impact on reducing the number of pregnant women and their developing babies who are exposed to Accutane.

In summary, the following are OTIS's recommendations.

Number one, increase regulatory safeguards concerning the use of Accutane in reproductive age women using the thalidomide STEPS program as a template to include: mandatory enrollment of physicians, pharmacists, and patients by the manufacturer; an improved monitoring system for reporting a greater number of Accutane-exposed pregnancies, including a substantial increase in the use of the patient survey; increased patient accessibility to the use of two reliable forms of contraception; continued educational activities provided for physicians, pharmacists, and patients concerning the teratogenic potential of Accutane.

In looking over the information we received on Friday, we were very pleased that many of these safeguards have recently been addressed by the manufacturer.

Number two, incorporate OTIS toll-free phone number and web site information in all Accutane packaging so that direct access to risk assessment and counseling concerning the use of Accutane prior to and during pregnancy is available to the consumer; amend marketing

strategies to include pregnancy warnings in all direct-to-consumer advertising; and continued evaluation of the effectiveness of this program and modification, if necessary.

Thank you to the committee for allowing me to speak.

I also don't know if anyone is interested, but unlike Dr. Jones, I don't usually read McCall's Magazine, but this is an example of the kind of advertising that we would like to see pregnancy warnings on. Would people like me to pass that around?

DR. BERGFELD: Are you through then?

MS. QUINN: Yes.

DR. BERGFELD: Thank you very much. We'll pass that advertisement around.

The next presenter, which is our seventh presenter, is Larry Sasich who is presenting as a public citizen.

DR. SASICH: Thank you very much for this opportunity to speak. My name is Larry Sasich. I work at Public Citizen's Health Research Group in Washington, D.C., and I have no conflicts of interest.

Public Citizen's apprehension over the safety of Accutane began shortly after its approval in May 1982 when we petitioned the Food and Drug Administration to take

immediate action to warn patients and physicians about serious adverse effects associated with the use of this drug in September 1983. The thrust of our petition was a request for a boxed warning on the possibility of birth defects, spontaneous abortion, pseudotumor cerebri, impaired vision, and regional ileitis caused by Accutane. In addition, we asked for the mandatory distribution by pharmacists of labeling written for patients, then called patient package inserts, explaining the risks of this drug in nontechnical language.

A final rule that became effective June 1, 1999, gave the FDA the authority to require patient labeling, now known as medication guides, for drugs that present a serious risk to the public health. Accutane is a drug that clearly meets this standard. An Accutane medication guide would inform patients not only about the risk of birth defects and the other adverse effects mentioned above, but also the possibility of neuropsychiatric adverse effects; erratic bone growth and premature closure of the growth plates; inflammation of the pancreas; elevations in triglycerides; hearing impairment; decreased night vision and corneal opacities; allergic reactions; and drug interactions, all now in the drug's professional product labeling.

It has taken some very dedicated people at the

Food and Drug Administration 20 years to get the first medication guide. We've only had one that was announced two weeks ago. Patients basically do not have access to objective risk information, readily available risk information about their prescription drugs.

On April 26, 1988, the FDA's Dermatologic Drugs Advisory Committee recommended, without specifying a method, that the prescribing of Accutane be restricted. Shortly thereafter, we again petitioned the FDA on May 17, 1988 to limit the prescribing of the drug to board-certified or board-eligible dermatologists. Dermatologists would have been required to register with the FDA and assigned a prescriber number. To prevent the off-label use of Accutane, dermatologists would have been required to certify by affidavit that they had read and would follow the regulations and the drug's approved labeling. Pharmacists would have been prohibited from knowingly filling prescriptions from physicians who were not dermatologists registered with the agency. Both physicians and pharmacists would have been subject to criminal penalties for violating the regulations. A copy of our 1988 petition is attached to these comments for your reference.

We believe that the legal theory outlined in our 1988 petition shows that the FDA then had the authority

to require the restrictions outlined above and that this theory is as sound today as it was 12 years ago. In fact, since our 1988 petition, there have been several recent examples of the creative use of the Food, Drug and Cosmetic Act to place limitations on the use of certain drugs in a manner consistent with our petition.

To reduce the chance of potentially life-threatening agranulocytosis, the original labeling for the antipsychotic drug Clozaril required "a baseline white blood cell and differential count before initiation of treatment and a white blood cell count every week throughout treatment," and that "the distribution of Clozaril is contingent upon performance of the required blood tests." Clozaril was approved September 26, 1989.

The approved labeling for thalidomide, a drug cleared for marketing on July 16, 1998, requires that only prescribers and pharmacists registered with the System for Thalidomide Education and Prescribing Therapy Program, or STEPS, are allowed to prescribed and dispense the drug. Also, "patients must be advised of, agree to, and comply with the requirements of the STEPS program in order to receive product." Thalidomide and Accutane are drugs that may have very similar risks in causing birth defects.

The use of trovafloxacin, a fluoroquinolone antibiotic approved in 1997, was restricted to hospital or

long-term nursing care facilities on June 9, 1999 after reports of serious liver injury.

The labeling for the antiarrhythmic agent dofetilide, or Tikosyn, approved on October 1, 1999, states that it is "available only to hospitals and prescribers who have received appropriate Tikosyn dosing and treatment initiation education."

In addition to requiring a medication guide for Accutane and the restriction of the drug's prescribing to FDA-registered dermatologists and to its labeled use, the FDA must require a postmarketing study to determine if these interventions will have met the agency's goals as stated in the questions to this committee: no patients beginning the drug if they are pregnant and no pregnancies occurring while on Accutane treatment. This study protocol should be approved by the FDA's Office of Postmarketing Drug Risk Assessment. At a minimum, the study should last one year and include evaluation of requirements that only a limited supply of Accutane is provided to women and that the drug is not provided without proof of a negative pregnancy test. The precedent for this latter requirement is the Clozaril "no blood, no drug" policy mentioned above.

Public Citizen believes that Accutane is a beneficial drug when it's used for its approved indication. However, if the combination of a medication guide and the