prescribing and dispensing restrictions mentioned above cannot be shown in a postmarketing study to meet the agency's no-pregnancy goals after one year, the drug should be withdrawn from the market.

Continuing medical education programs, professional product labeling changes, and optional patient information brochures have been the Pavlovian response to drug safety issues by manufacturers and the FDA for years. It is time to admit that this is a failed paradigm and recognize that rigorously enforced regulation may be the only way to ensure that patients are informed and that drugs are prescribed appropriately.

I was very pleased to listen to the comments by Dr. Peter Honig from the Office of Postmarketing Drug Risk Assessment. I think this is the first time that I have so clearly heard anyone from the Food and Drug Administration say that labeling changes and the like have failed.

Where industry interests have been at stake, the FDA has been innovative in interpreting the Food, Drug and Cosmetic Act to get drugs such as clozapine, thalidomide, and dofetilide on the market. It's time for the agency to use the same creativity to protect the public's safety.

We hope that it will not be necessary to return to this committee in the future to discuss how to reduce

Accutane's risks to patients.

Thank you very much for your attention.

DR. BERGFELD: Thank you.

Our eighth presenter, Dr. Nancy Green, Associate Medical Director, March of Dimes.

DR. GREEN: Thank you. Thank you for the opportunity to address this committee today. As you just stated, my name is Nancy Green. I'm the Associate Medical Director at the March of Dimes. I'm also on the faculty of Albert Einstein College of Medicine where I'm an assistant professor of pediatrics and cell biology.

I'm going to just tell you that neither I nor the March of Dimes has any conflict of interest here.

I'm going to give you the bottom line of my comments and that is that despite current voluntary safety measures taken by the manufacturer of Accutane, many pregnant women and their developing fetuses are unnecessarily exposed to this drug and major birth defects have developed in these babies. We recommend a more stringently monitored and restricted mandatory system for clinical use of Accutane such as the system currently in place for thalidomide.

So, just to remind you, the mission of the March of Dimes is to improve the health of babies by preventing infant mortality and birth defects.

You've heard several descriptions of the teratogenic effects of Accutane, and I'm just going remind you then briefly of those. This is a syndrome coined "Accutane syndrome" described by Dr. Lammer about 15 years ago, and we're talking about major defects, as Dr. Lammer very nicely described, in the central nervous system, hydrocephaly, microcephaly, and mental retardation. And as Dr. Adams suggested, I think that the extent of mental retardation, sometimes more subtle than is apparent at birth, is just being appreciated.

There's also craniofacial defects, most commonly cleft lip and palate, and as you saw, also ocular defects. There are also cardiovascular anomalies. Some of these have been reported as being very serious and proving fatal in the newborn period. There are additional birth defects as well associated with limb defects, eye defects, and thymic development. As you've heard as well today, there's a substantial increased risk of miscarriages in women who take Accutane early in pregnancy. Again, I remind you, as Dr. Lammer said, many of the women taking this drug do not know they're pregnant because the effects of Accutane are most profound in fetuses early on in pregnancy, certainly well within the first trimester.

This is our position on Accutane. As you've heard, Accutane is potent teratogen. I think that's an

indisputable fact. This is not a minor problem. It's been estimated in various studies that you've heard today -- and I will not recite them again -- that anywhere from 25 to 35 percent of fetuses exposed to Accutane early in pregnancy are affected by major defects. In fact, as Dr. Lammer suggested, this is analogous best to thalidomide, and I don't think I have to describe the thalidomide effects to this group, but just to say that before the effects of thalidomide were appreciated, 10,000 children were affected by thalidomide. 10,000. So, we would hope that this would not happen with Accutane.

Again, as you've heard, many fetuses are at risk. Dr. Mitchell described his extensive survey of half a million women who are prescribed Accutane, who take Accutane, and again as you have heard, that only represents approximately 40 percent of total women. So, if you do the math, it comes out to about a million women in the U.S. are exposed to Accutane.

In fact, again as Dr. Mitchell has said, about 1,000 pregnancies have occurred in women taking Accutane, and again that represents only 40 percent of the total.

Again, as you've heard, birth defects have occurred. This is not a theoretical concern. This is a major public health issue when you consider the number of women taking Accutane in childbearing age.

The March of Dimes advocates a strict monitoring system for oral Accutane similar to the program that is used for thalidomide. Again, you've heard that, but I'm going to just reiterate some of the points about the STEPS program administered by Dr. Mitchell for thalidomide, and that is mandatory physician registration, mandatory pharmacist registration, and mandatory patient registration, monthly pregnancy test, and frequent follow-up and education.

So, I echo the concerns that have been described earlier of the limited registration in the Slone study, and we would like very much for the FDA to approve mandatory registration like the STEPS program. I would like to say, by the way, that I don't have the most recent numbers and I hope that Dr. Mitchell could supply them. But the thalidomide STEPS program started in July of 1998, and as of August of 1999, there were several thousand people registered to use thalidomide in this program, of which about a third of those were women in childbearing age. And to date, according to the Thalidomide Advisory Committee, there have been no breakthroughs with thalidomide. So, that stands very much in contrast with the Accutane experience.

Thank you.

DR. BERGFELD: Thank you very much.

We have two remaining statements. They are both written. The first is from Randall Warren, the CEO of the Thalidomide Victims Association, and his statement will be read by the Executive Secretary.

MS. TOPPER: "To the Attention of: the Dermatologic and Ophthalmic Drugs Advisory Committee.

"Reference: Meeting of September 18-19, 2000 to consider NDA for Accutane."

"Thank you for the opportunity to submit a written statement regarding the NDA for Accutane.

"The Thalidomide Victims Association of Canada (TVAC) was created in 1988 to "empower and enhance the quality of life of Canadian thalidomiders." Since 1995, the Association has been forced to undertake a second mandate, "to ensure that a tragedy as occurred with thalidomide in the late 1950's and early 1960's will never happen again."

"Thalidomide is arguably the most notorious pharmaceutical disaster in world history, thankfully avoided (for the most part) in the United States. 10,000 to 12,000 babies were born worldwide with severe birth defects, of which 5,000 survive today. No one will ever know how many babies were never born or were stillborn.

"The world believed Thalidomide was banned. The world was wrong. The drug continues to be used. In

1998, thalidomide was licensed in the United States. It became the strictest regulated drug in US history under a program developed by a drug company to prevent foetal exposure. This was a new system, called STEPS.

"Why was a system developed? The answer is simple, because none of the other systems designed to prevent foetal exposure to teratogenic drugs were successful, including the voluntary compliance system of Roche for Accutane. To this date, no foetal exposures have occurred with thalidomide (in two years) under the mandatory compliance system called STEPS.

"In a presentation to this very committee, three years ago, I stated the position of the Thalidomide Victims Association of Canada. Although appalled that licensing of thalidomide was even being considered, thalidomide victims were forced to prefer licensing as the most secure way to ensure no more babies would grow up seriously disabled. Thalidomide victims also felt that they could not deny the drug to those suffering and dying from horrible conditions. The major request of the victims of thalidomide was that if thalidomide was to be licensed, it had to be done under a mandatory compliance system. This was not an easy position to take as can well be imagined.

"Although isolated for over 35 years from

society, the Association's entrance into the issue of thalidomide licensing thrust us into the world of all teratogenic drugs and their management.

"Have any lessons been learned from the tragedy of thalidomide yesterday and the management of thalidomide today?

"We believe the answer must be yes, or our very presence in very difficult circumstances would be for naught. We believe that the mandatory compliance system demanded by the FDA for thalidomide licensing was the herald of licensing requirements for all teratogenic drugs. Although no system is foolproof and there will be incidents and suffering, voluntary compliance systems are even more dangerous and certainly less consistent.

"It is not the business of the Thalidomide Victims Association of Canada to determine whether the risks of the drug are outweighed by the benefits. That determination must be left in the hands of scientists and professionals such as this committee. It is the business of the Thalidomide Victims Association of Canada to remind those making these decisions that the risks can always be lessened by responsible thinking.

"The very population that Accutane is designed for, and the off label availability of the drug when licensed, necessitate a mandatory compliance system. We

used Accutane as the example of our argument for mandatory compliance for thalidomide use. While a mandatory compliance system will not totally eliminate the risks, it will lessen them, and offer consistent warnings and education to vulnerable patients. If mandatory compliance lessens pain for just one family, creating one less victim, it is worth it.

"No amount of compensation can compare to a healthy able bodied body.

"Once again, we trust the wisdom of this Committee to do the right thing and remember victims of the pharmaceutical disasters everywhere. You can make a difference, not only for those who may be given Accutane, but for all future teratogenic drug licensing applications.

"With Respect, Thalidomide Victims Association of Canada, Randolph Warren."

DR. BERGFELD: Thank you. Our last presentation in this public forum is from Dr. Steve Webster, former President of the American Academy of Dermatology. This is also written and will be read by the Executive Secretary.

MS. TOPPER: Dr. Webster had intended to attend but, unfortunately, had a family emergency. So, his talk is like him reading it.

"My name is Stephen Webster. I am a past

secretary-treasurer and past president of the American Academy of Dermatology and a clinical professor of dermatology at the University of Minnesota Medical School. More importantly, I am in the clinical practice of dermatology at the Gundersen Lutheran Medical Center in La Crosse, Wisconsin. In my clinical practice, I take care of many acne patients and particularly young adults in their 20s and 30s who have severe cystic acne, a condition which is difficult to control and which occurs at a time in their lives when cystic scarring acne can significantly affect their careers and future. The only medication to safely and effectively control their disease is Accutane. Without easy accessibility to Accutane, these patients would require high doses of antibiotics which less effectively control the acne and have the potential for significant side effects. May I give two examples.

"A 22-year-old female graduate from college with a marketing degree has active cystic acne. She is facing several job interviews with marketing firms. However, her cystic acne is quite prominent, and in the marketing world, this severely hampers her chance at a position. This acne scars more than her skin, it also scars her self-image. She is willing to follow all precautions to prevent pregnancy while on the medication. She requires ready access to Accutane through a physician.

"Similarly, a 24-year-old investment banker with severe cystic acne. Confidence in an investment banker by his/her clients is essential. The marked facial acne cysts with a potential to scar make it difficult for him to establish his credentials. It is not a laughing matter, but will people invest their money with someone with an 'adolescent' disease like acne. Again, his life is significantly affected.

"Both these patients require Accutane for safe efficient control of their disease. An informed motivated patient with instruction, direction, and proper laboratory and dosage control by a physician can be successfully treated with Accutane. In a smaller town, such as La Crosse, restrictions on physician prescribing and pharmacy dispensing of Accutane would be unfair to this group of patients. The effects of cystic scarring acne in any patient, but especially in young adults starting their careers, can be extensive and go beyond the skin by affecting their lives. We need access to this medication. Dermatologists have proven they can safely provide this important medication to our patients.

"On behalf of our patients, I thank you for your consideration.

"Stephen B. Webster, M.D."

DR. BERGFELD: We have had no additional

requests for a formal presentation, a public presentation, so we'll go on with our meeting.

Because we had to cut the questions a little bit short after the Roche presentation, I would like to ask the committee members if there are any questions for clarification that could be asked at this time. Dr. Miller?

DR. MILLER: I wanted to ask Mrs. Leach, when you gave the presentation this morning, if the physicians whom you contact who have prescribed Accutane don't respond to you, what course might you take? Or how do you handle that specifically non-dermatologists?

MS. LEACH: Oh, the non-dermatologists. We invite them to call us, and I have to tell you that I don't have the figures at hand, but of the physicians that we send the message to, 90 percent of them do call. I don't have a slide to back that up. It's anecdotal, but I check them off my list.

DR. MILLER: One other question. With the prescribing on a month-to-month basis, is there any problem with any of the prescription plans where only 90 days are administered? Or can arrangements be made, or is that a problem?

MS. LEACH: Actually it isn't a problem because an exemption is made for Accutane. We've already worked

that out.

DR. BERGFELD: I have one other request.

DR. CRAGAN: Jan Cragan. I had a question probably for Dr. Webster.

I wanted to know if there is any information about the proportion of patients who require more than one or undergo more than one course of treatment with Accutane, how long they would roughly go in between courses, and if there's information about the pregnancy rates with subsequent courses compared to the first course.

DR. WEBSTER: Taken in reverse order, there's no information about pregnancy rates with retreatment that I know of.

The time between initial treatment and retreatment all depends on what the patient does when he's taken off the medicine. If there's a rapid nodular flare of acne, the prudent thing would be to pop the patient right back on Accutane.

The percentage of retreatment depends roughly on the dosage of drug given and the duration. If you give a milligram per kilogram per day for 4 to 6 months, roughly 80 percent of patients need no retreatment again and have no significant acne again.

DR. BERGFELD: Dr. Woodcock?

DR. WOODCOCK: Yes. I had a couple questions

about the educational program that's currently going on with Accutane for Roche, if I may. They're just clarification questions.

Does it involve physically visiting the prescribers?

MS. LEACH: Yes. Actually the Roche professional representatives actually go out. During the next couple of months, we're going to be going out to implement the office implementation strategy.

DR. WOODCOCK: Yes, that's what I gathered.

Do you visit prescribers in small towns?

MS. LEACH: Yes. In fact, the representatives cover about 90 percent of the prescribing dermatologists.

DR. WOODCOCK: So, Roche would have physical contact basically with prescribers.

MS. LEACH: Yes.

DR. WOODCOCK: And then you said you intended to have the same interaction with non-dermatologist prescribers. Would that also include physically visiting the offices?

MS. LEACH: We're still trying to work out how that would be accomplished because some of them are in very remote areas, and we're hoping to do either video conferencing or teleconferencing.

DR. WOODCOCK: Thank you.

DR. BERGFELD: Dr. King?

DR. KING: My question is really more the extent of data. Since the thalidomide problem was identified in Europe, I wonder if there are data from the European and other countries where Accutane is prescribed. If they don't have this same kind of pregnancy prevention, one would like to know what happens in those places. There must be lots of that prescribed, and if you're worried about offshore prescribing and other alternative sources, it seems to me that may be part of the problem.

DR. ELLISON: I think there are two parts to the question. The first is what's the experience in pregnancy rates and pregnancy reports in Europe. The problem is it's very noncomparable. All we have is spontaneous reports, number one, from which it's very difficult to establish a rate because of the total lack of knowledge of under-reporting.

The second issue is we do not have very good estimates of use. We don't have the prescription monitoring services in Europe that we have in the United States with the exception of IMS, which covers a very narrow panel of dermatologists there. Most of the use data we have to get from factory shipments. So, we end up with a spontaneous report number over factory shipments. So, really it's very difficult, and it always has been for us,

to calculate a rate for Europe. It would have been theoretically good to know something like that because, as you say, you could compare, but unfortunately, it's been absolutely impossible. All we have is spontaneous reports.

The reporting system there is very different as well. The MedWatch program in the United States has made an enormous difference in the quality and quantity of reports that we get here. So, I think we have someone here who could probably speak further to it, but there's very little that we -- he has had to leave.

DR. BERGFELD: Do you need further clarification?

DR. KING: Actually I'd like clarification of the reverse question to that. If there is a group like OTIS keeping up with a benchmark of how many teratogenic effects, has that been increased? You can't bring Accutane with all the complications, but it seems like there would be a registry for the number of children who are having increased malformations. Maybe they're not as dramatic as thalidomide, but it seems to me that there would be some data on a baby with no ears and so forth and so on. You're saying that's not possible?

DR. ELLISON: You mean in Europe?

DR. KING: Right.

DR. ELLISON: From the pregnancy registries in

Europe, we haven't really seen much data that would tell us much about retinoid malformations, unfortunately.

DR. BERGFELD: Dr. Mills?

DR. MILLS: This is a comment primarily for the Roche people. Despite the considerable efforts on the part of the Slone Epidemiology Unit and Roche personnel, as an epidemiologist, I'm not confident that they can accurately estimate pregnancy rates, nor that they have the data to determine if the rates are, in fact, falling.

The data that were presented to show the rates are from two sources, the first being spontaneous pregnancy reports, and the FDA staff noted that these tend to be very poor because of incompleteness of reporting. In fact, if you look at the slide Dr. LaFlore presented, his page 9, the rates of spontaneous pregnancy reports on his slide are 0 per 1,000 patients all the way through from 1991 to 1998, which gives you an idea of the tremendous under-reporting problem and the difficulty in determining that rates are dropping from that type of information.

The second body of data that they used for these conclusions were, of course, the Slone Epidemiology Unit study. I'd point out again that by the Slone estimate, 55 percent of the women at risk did not provide information for that study. By the FDA estimate, 60 to 70 percent of the women at risk did not provide information.

So, we don't know if those women were getting pregnant or not.

Now, Dr. Mitchell, as a good epidemiologist, recognizes that it's very difficult to estimate a pregnancy rate in a group or a change in pregnancy rate in a group where you don't have information in 50 to 70 percent of the people in that group. He has tried hard to determine whether those 50 or 70 percent of non-participants are similar to the people who did participate. However, he did not have the necessary authority to get the information by which I mean that he would need to contact a random sample of the women who elected not to participate in order to really know if that group is similar to the group that did participate.

A lot of epidemiology is sort of common sense. If those of you who are M.D.s in practice think about this, imagine that you have two women in your practice, one who was a typical noncompliant patient who's likely to miss doses of her oral contraceptive or to have unprotected intercourse and is, of course, in this instance the most likely to get pregnant. The other patient is the woman who's extremely compliant and very reliable and very unlikely to get pregnant. Ask yourself the question, which of those two women is more likely to volunteer for a survey for questionnaire and follow-up? I would suggest that it

may well be the compliant women which would lead to a gross under-estimate in the percentage of women getting pregnant.

So, in conclusion, to get accurate information on pregnancy rates and to determine if, in fact, the prevention strategies are working, it's necessary to have the entire population in hand so that you can see how many women really are getting pregnant.

The only alternative that would be a second-best choice would be if someone had the authority to require a sample of non-participants that would be random and representative. You might be able to get the data like that. But obviously, that's extremely difficult for legal and technical reasons. So, if you want to answer the question of are there pregnancies and are you preventing pregnancies with your programs, you have to have the women and be able to study them.

DR. BERGFELD: Thank you.

Dr. Woodcock?

DR. WOODCOCK: I just wanted to make a clarification. It's my understanding that the European system of distribution and actually the utilization in Europe is quite different than in the United States in general. Is that correct?

DR. ELLISON: Sorry. In the sense of?

DR. WOODCOCK: Of course, Europe has a very

different health care system than we do from country to country, and who is authorized to prescribe drugs may vary. My understanding is that is the case with this drug.

DR. ELLISON: Yes. The one example that I know of is the limitation to dermatology practitioners in the United Kingdom. I'm not quite clear at the moment of what the status is in France, and elsewhere it does vary.

DR. WOODCOCK: So, my point was simply clarification, that any information from Europe may not be directly applicable to the U.S. situation because the Europeans have various restrictions or whatever on the distribution of this drug.

DR. BERGFELD: Thank you.

Dr. Wilkin?

DR. WILKIN: Yes, that was my point as well. While I don't really have up-to-date information on distribution, I have a Lancet report of 1988 which says that in Australia, Finland, and Israel, only dermatologists prescribe Accutane or isotretinoin; that in England, Wales, Czechoslovakia and New Zealand, it only comes from hospitals; that in Norway, it requires authorization from a health department; and in Italy, it's males only. So, the point is well taken, that it's apples and oranges.

DR. BERGFELD: Dr. Branch, then Dr. Rosenberg.

DR. BRANCH: I'd like to go back to the issue

of differential risk. Are there at-risk groups of individuals? I was a little confused trying to link pieces of the information that came through in the presentation of the Slone Epidemiology data. If I recollect rightly, there was 25 percent of the children who were born following exposure had not had any form of contraception, and yet there's a slide that came much earlier that suggested that about 1 percent, if I recollect, of women who actually said, no, they were in the reproductive age and they had a very small incidence.

So, is that a target group that can be more easily identified? If you have a target group, is it appropriate to develop a special strategy for them if they can be identified up front? I'd appreciate some clarification.

DR. MITCHELL: I think Dr. Vega phrased it very aptly when she said abstinence can change overnight. What we identified in our data was that there was only a fraction of women who reported that they were sexually active and not using contraception. That was the 1 percent figure.

What we find is that among the women who become pregnant, not surprisingly, there was one or more opportunity where there was sexual activity without contraception. As I understand the objectives of Roche,

one of the objectives is to increase the communication between the doctor and patient to identify those patients but also to identify to those patients the nature of the risk. And that's the whole point of the contraceptive counseling, that there's a lot of sort of bravado among non-contraceptors who are sexually active or women who are not sexually active and not contracepting. I think one of the targets is, indeed, just that.

DR. BERGFELD: Thank you.

Dr. Rosenberg?

DR. ROSENBERG: I had two questions. One was Roche also provided a drug called Soriatane, a highly potent retinoid used in the treatment of psoriasis. I wonder, are there any problems with Soriatane? Do you do anything special about Soriatane? And if there are no problems, why not?

MS. LEACH: Soriatane is indicated for severe psoriasis. The patients have a pregnancy prevention program, as we do for Accutane, and the age of the women who are taking it are a little bit older. In fact, the majority of them are not in their reproductive years, and with the same program, we've had no pregnancies or reports of pregnancies.

DR. ROSENBERG: The other question was before lunch I had touched on the issue of abortion. To back up

and as was just mentioned, does the counseling program now in place discuss morning-after pills?

MS. LEACH: The current label calls for a discussion with your provider if you should become pregnant. The new program puts us in a position of giving out emergency contraceptive information. It teaches physicians about it and the fact that it is not an abortifacient and it also gives information to patients as to what to do when they think or suspect that they might be pregnant.

DR. ROSENBERG: So, it specifically mentions the post-intercourse --

MS. LEACH: There's a section on emergency contraception.

DR. BERGFELD: Any other questions?

Dr. Epps and then Dr. Greene.

DR. EPPS: Actually I just had a brief comment. I was just curious. How long does it take to complete -- or have you timed -- the new packet? I know the video is about 4 minutes, but going through all those materials, how long does it take?

MS. LEACH: We've done some pilot testing and it actually takes a little bit shorter amount of time because of the organization that's been brought to it with the numbering system. The reps will be meeting with

prescribing dermatologists to help them to implement it. The dermatology nurses, as you heard very movingly from Nancy Vargo, are really very enthused to get into this and to help support the prescribers, and it actually took a little less time.

DR. EPPS: How long?

MS. LEACH: On average, the old was about 20 minutes and this comes to 15 minutes. It's not an enormous amount of cut of time, but I don't think time is the issue here. What is the issue is, do the patients really understand what you're saying and can they feed it back to you?

DR. EPPS: Yes, I agree with that statement too. However, there are some practitioners in the real world -- and I understand the importance of making sure that everyone understands what you're giving and what the patient is taking. But if you have an HMO that says you must see a patient every 7 minutes, every 10 minutes, and then you have an Accutane consultation, even whether it's spread out for a couple of sessions, that can be an issue and that may be a compliance issue as far as some physicians are concerned.

MS. LEACH: I couldn't agree with you more. As a practitioner myself and as a person who has actually sat down with a patient and gone through the pregnancy

prevention program, I know that this is time consuming. But I think that every one of us who has ever participated in the prescribing of Accutane understands that this is a very worthwhile thing. With the nurses and their enthusiasm to get into it, it serves as another person to back up the prescriber.

DR. EPPS: The second is just a comment regarding the pharmacies. Lately there has been a trend where either you do not speak to a human being, you leave a message on voice mail for a prescription, or especially in this area where there are mail order pharmacies in New Jersey and Florida especially in this area, but also in other parts of the country. That can be an issue. Certainly it's up to the practitioner to set forth their limits, but oftentimes patients will request medications three months at a time or refills. Certainly it's up to the practitioner. But there are some pharmaceutical issues which are affected by the suggestions that have been made.

DR. BERGFELD: I think that's a statement rather than a comment, Dr. Epps?

DR. EPPS: Yes.

DR. BERGFELD: We have three other people who have asked to speak and perhaps more. Drs. Greene, Moore, and Branch. We'll take them in that order.

DR. GREENE: I have a couple. As the

obstetrician in the crowd, I feel obligated to point out that, Ms. Leach, on the slide on page 7 there, there are about 4 million births in the United States per year, and your Venn diagram indicated only 3.6 million pregnancies. So, I'm not sure where your numbers --

MS. LEACH: Can I admit that I made a typo? It's supposed to be 6.6.

DR. GREENE: Okay, thank you.

MS. LEACH: Dr. Westhoff pointed that out to me this morning.

DR. GREENE: If you could just stay at the podium for a minute, I have another couple questions about your presentation.

On your slide at the top of page 9, you mentioned that 91 percent of surveyed women believe they know about contraception, and yet 37 percent choose the least effective method of birth control. Do we have any insight into why this happens, why these women choose less efficacious methods of contraception?

MS. LEACH: Could I be permitted to introduce Carolyn Westhoff who is an obstetrician/gynecologist and has more insight into that?

DR. BERGFELD: Yes, to address this.

DR. WESTHOFF: Thanks, Eileen. Eileen called on me a while ago as a content expert in contraception, and

I do a lot of contraceptive stuff.

I think over the last couple of decades, women choose less effective contraception because they don't understand the risks very well, and particularly because women in the United States have become very fearful of the more effective methods because there's an exaggerated notion of the side effects.

I want to just plunge in and say that I think the enhanced program will have a number of things going for it from changes in the environment over the last decade, and one is that we have new safety data and people are getting more realistic about the highly effective methods. We have new highly effective methods available. So, it's a matter of educating people about that and emergency contraception is available.

Something that was not available to the old education program were the urine pregnancy tests that are highly sensitive that can be done immediately in the doctor's office or by the patient at home. Those were not available when this program was introduced a decade ago.

Finally, one sort of outside bonus for the new program is the reputation of oral contraceptives has gone way up since it received the acne indication. That's something that's probably going to be very synergistic for this setting because you actually saw the women enrolling

in the survey are much more likely to be using the pill over the last couple of years. So, I think there are a lot of changes in our contraception environment in the last decade that will work in favor of this enhanced program, and that's an important point for the committee.

Thank you.

DR. GREENE: Two more.

DR. BERGFELD: Go ahead.

Thank you.

DR. GREENE: On your slide on page 21, you mention a dermatology resident program. I assume that's an education for residents in dermatology. Could you describe a little bit about the content of that?

MS. LEACH: That's correct. Every July, the Roche representatives go to the new residents who have come into the program and present the pregnancy prevention program. We actually use a video to show a scenario of an exchange. Recently I've been going to the residency programs to bring them up to date. I've been to the University of Colorado in May and Wisconsin in June, and I'll be doing the Columbia Physicians and Surgeons in October. But we intend to be able to go to every dermatology residency program to make sure that the new dermatologists are also as experienced as the old when they go into practice.

DR. GREENE: And one last question, please. I was surprised in June when the 4-minute videotape showed up at my office. I've never prescribed Accutane. Could you tell me who you sent that video to?

MS. LEACH: We sent that video to all dermatology prescribers, but when we had sent the Dear Doctor letter, we had also informed obstetricians and gynecologists about the changes in the label. To be truthful, the two lists were used, so every dermatologist got it and every obstetrician/gynecologist got it and every pediatrician. So, it's had a wide circulation, a little wider than we had anticipated but it's non-branded, so it was okay.

DR. BERGFELD: Thank you.

Dr. Moore?

DR. MOORE: I have just a comment and then a question for Dr. Mitchell. This is concerning the responsible prescription of this drug. I guess when I look at what I consider sort of skyrocketing prescriptions of the drug, I'm not so convinced that it's all for severe acne, especially when you look at the recent dermatology literature when there are quotes like not only to patients with severe disease, but also to patients with less severe acne when they're describing prescribing practices and prescribing it sooner rather than later.

I was just wondering in the program in the survey, Dr. Mitchell, is there any way that you can get at the indication for the drug use, and if there's not now, are there any plans to do that in the future or in any feedback given to physicians who may not be using this responsibly?

DR. MITCHELL: It's a great question, Dr. Moore, and one of the major benefits of having our own advisory committee was to be able to bounce off the committee suggestions like that, which was in fact one of the early suggestions in the survey. Despite some counsel from people who knew better on our committee that we would not get useful information by asking patients to describe the severity of their acne, we tried, and it was a dismal failure and we abandoned it because, as has been described and as people like Rob Stern who have done so much of this research will point out, patient-described acne is very, very non-specific. So, I'm afraid that we're not going to be any help there. I don't think the survey offers that opportunity.

DR. BERGFELD: Anything else?

DR. MOORE: I'm just wondering how about from the sponsor? Is there any way to get this information?

DR. ELLISON: I think it would be very useful in our discussions about how much Accutane prescriptions

are outside the indication to get a precise idea of this, to have some direct assessment. I think the indirect ways we have remain indirect and they're only samples.

So, the opportunities we have have to be limited to find a way to directly observe or to have a very structured discussion with a physician about what they have. The only other way is to survey acne patients as they're being treated because once you've had Accutane, then you will no longer have severe recalcitrant acne. And it's been something that we've been struggling with over a while.

One of the things, in terms of intervention that we can do, not with I think treating less than severe acne, but in treating in pregnancy prevention is in the 10,000 calls that we get per year about Accutane, it's an opportunity to discuss with patients and their providers if they are, indeed, compliant with the PPP program, and if they are not, to take that opportunity to remind them, but also to add that practitioner to the representative education one-on-one, implement the office system if that hasn't happened.

We are looking at ways of trying to use that also, at least with practitioners, to discuss their practice patterns with severe recalcitrant nodule cystic acne to see if we can get a better handle on it.

DR. BERGFELD: Dr. Branch is next and then Dr. Jones.

DR. BRANCH: As a comment to the last question, wouldn't it be reasonable if you could really reduce the risk of pregnancy in these people, you might substantially improve the therapeutic window, and in fact you could extend the range of value of this drug to a far larger group of patients and thereby not only enlarge your market value but actually help a lot more people, but it's on the proviso that it's done in a safe factor? That's more in the line of a comment.

DR. ELLISON: Our view on this is we really think that the role of Accutane is in nodular acne, or if you put it in a larger context, and the reason is because that's what scars, that's what causes the permanent sequelae and disfigurement. There are alternatives that don't have this risk. Even if a program could guarantee no risk, certainly a drug that causes no risk would be better. So, it's really our interest, and indeed, we do try to limit it to those patients who really do have no alternative in the sense of making this kind of difference.

DR. BRANCH: If that's true, we've had an advertisement that was circulated just a few minutes ago, if you look at the picture of the boy on that advert, would you classify that as severe nodular acne?

DR. ELLISON: No, we wouldn't, and in fact, we deliberately did not do the disease ads, if you will, using severe nodular acne precisely because we didn't want to connect this, if you will, with Accutane.

DR. BRANCH: My question actually, before I got into that sideline, was more related to an aspect of trying to develop a process of helping educate patients. There was a slight discrepancy between what was said by Nancy Vargo and what was provided in the written material. But my attention was brought back to it by the comments just a moment ago about the enthusiasm the nurses have for being able to promote an anti-pregnancy problem. What is actually written in her statement here is, "but they are clearly not aware that there's a pregnancy problem with Accutane." There appears to be a bit of a discrepancy here.

There's a whole process that takes place in terms of informing patients, and it seems to me that nurses and pharmacists have been left out of this plan that you've proposed. It seems that all the support structures in the health care system could really be used with benefit to try and promote it.

DR. BERGFELD: Would you like to respond, Ms. Vargo?

MS. VARGO: I would like to clarify that

statement about clearly nurses do not know that there's a pregnancy problem with Accutane. We clearly do know what the results of Accutane are on a pregnancy, and that really was more reflective of the survey that I sent out. How I meant to word that was that our nurses seem to be very, very proud of what they are doing and they seemed to be unaware that the issue of pregnancy is still occurring as an issue. In other words, we know the harm that Accutane can have on a pregnancy, but the issue was that they didn't feel that there was a problem. They all felt that their role and their dermatologists were doing a really dandy job. To tell you the truth, the system is highly effective.

DR. BERGFELD: Thank you.

Dr. Jones?

DR. JONES: Yes. I want to say that I'm really very impressed with the collaboration that clearly is going on by the dermatologists in this country and Hoffmann-LaRoche as far as the educational programs, et cetera.

But one of the things that I think really is incredibly important in terms of the deliberation of this committee relative to mandatory registration relates to the issue of all the other people that prescribe Accutane. What I mean by that is all the other physicians that prescribe Accutane. I am really unclear. I hear time and

time again, as you folks have been discussing this today, about all the wonderful things that you are doing with dermatologists, and it sounds great. It really does. But I am very concerned about the other physicians who clearly are prescribing Accutane who it seems to me are very, very clearly slipping between the bars here. Could you comment on how you plan to deal with this issue?

DR. BERGFELD: Could you briefly comment on it, Dr. Ellison?

DR. ELLISON: Yes. First of all, 85 percent of patients are coming from dermatologists, 15 percent of patients from non-dermatologists. Of the non-dermatologists, there is a spread of folks that probably prescribe about once a year, and we think it may be in response to a dermatologist's initial prescription. And then there is a more limited number who, indeed, have a higher prescription rate, and we've identified about 400 so far, and they're being added to our personal representative call and introduction to the office system and invitation to be registered with respect to having had their CME.

The others, all of them in the entire family practice, are going to get the non-personal communication, and we are over the next six months going to look at those 10,000 calls we get a year -- and 4,000 in the last four months or so -- to see if we can identify precisely those

practitioners who have not -- well, even the ones who have, but certainly ones who have not so that we can add them to that list. That is really what we're trying to do.

DR. BERGFELD: Thank you very much.

We have two more questions and then we're going to close down this clarification question time. Dr. Anderson, first.

DR. JENNIFER ANDERSON: Yes. I have a question about the new PPP. I assume at this point it hasn't actually started. Step 6 for the survey enrollment form seems to preclude patients enrolling in the survey by enrolling from the package. There's no longer going to be a form in the package of the pills so that they can enroll on their own?

MS. LEACH: No. There will continue to be a form in the package.

DR. JENNIFER ANDERSON: Because the way it's worded, you do not agree right at the moment and so that's the end of it.

MS. LEACH: As you see, that's a draft and has not been reviewed by Dr. Mitchell yet. So, that's why we haven't addressed that situation yet.

DR. BERGFELD: Thank you.

Dr. Greenhill?

DR. GREENHILL: Dr. Greenhill from Columbia

University.

Just two questions of information that would help me think about this. One is, is there a marketing plan for the sales representatives to visit the offices of a wide variety of different practitioners, primary practitioners, family practitioners, as well as dermatologists with Accutane, and are samples of Accutane permissible? I know they're not allowed with cII's, but I wondered if samples are distributed during those visits and what kind of information they include in terms of pregnancy prevention.

DR. ELLISON: In answer to your first question, which is similar to Dr. Jones' excellent question, we intend to start with where most of the prescriptions are coming from, and that would include also higher prescribers who are non-dermatologists and then work our way down. That's the first point. But certainly our metrics that we've given you is those high-prescribing non-dermatologists and the dermatology community.

The second point is we've never sampled Accutane and never will.

DR. BERGFELD: One more.

DR. ROSENBERG: A brief one. A question to Dr. Ellison. You've indicated that for reasons that you told us, that you think a formal registration would be less

desirable then an educational program such as you're starting. What's your feeling about an FDA patient information sheet, such as we've heard about?

DR. ELLISON: I think that's a very good question. We think this has been basically a very good innovation. We certainly think that the idea of objectivity is important. The idea that this comes from the government is important so that it's perhaps believed more and paid attention to more.

I think the key issue is going to be actionable content, to put things in there that are really important that the patient does and that really alerts them to the things that are most important to understand about this drug. So, I think if a medication guide would help in the sense of preventing pregnancy, then we would be very happy to talk about that with FDA and see them implement that.

DR. BERGFELD: I'm not going to take any more questions, and I'm going to adjust the agenda just slightly. We'll go forward with Dr. Vega's presentation. Much of the discussion or hopefully much of the discussion that we would have had planned afterwards somewhat must have been met during this discussion period. Then we'll move on to the questions. But we will have a break after Dr. Vega's presentation for 15 minutes.

Dr. Vega presenting on potential design

elements.

DR. VEGA: Before we go on to the different alternative designs, I would like to remind everybody why are we here, specifically why are we looking at this issue now.

We already saw the data we presented from the Slone this morning, and I believe that the rates are not the issue specifically that we want to address. We can see from that slide that although the rates over time are going down, the number of pregnancies are increasing.

This is the data that we are seeing here at the FDA. So, we can see that our concern is that we are still seeing pregnancies in spite of the rates going down.

What do we do? We ask this question when we are still receiving these reports of pregnancy exposures. As you will see now, the label is already really crowded. The box warning is two-and-a-half pages long with multiple bolded areas. This is just to illustrate what the Accutane label looks like. What else can we do to that label? It's hard to appreciate the bolded areas, but it's already two-and-a-half pages long.

We feel that other methods to communicate the risk are required. Other processes need to be implemented to communicate this risk and to manage this risk. We have learned that incremental changes in labeling and

communication have been relatively ineffective in the past.

Why do we need to revise the existing pregnancy prevention program for Accutane? We have already seen that the use of Accutane among women of childbearing potential is escalating. In spite of all the sponsor's and the agency's efforts to communicate Accutane's teratogenic potential to patients and their physicians, there is still limited compliance, as I mentioned this morning, with pregnancy testing before exposure, pregnancy testing during exposure, and the appropriate use of contraceptive methods.

We have also seen that the measures of pregnancy exposure and outcomes obtained from various sources are still very vague and that an increasing number of women exposed to Accutane will consequently increase the absolute number of pregnancy exposures. So, that is what we are looking at, the absolute numbers, and that's why we are here today.

The first step in engineering a risk management program for Accutane is to establish a set of goals. We have identified the following goals. Number one, no one starts Accutane if pregnant, that pregnancy must be avoided during Accutane therapy, and that an effective monitoring system must be in place to assure that these goals are met.

We will be discussing five different alternative program designs to help us achieve these goals.

Each one of these designs will be judged by their potential to achieve these various goals.

A well-designed pregnancy prevention program should at least take into consideration the following elements: education and informed consent, participation and tracking of pregnancies, compliance with pregnancy prevention practices, and the potential benefits of restricting drug distribution. These are the building blocks that we will be employing to construct various designs of a pregnancy prevention program for your consideration.

The first element to consider is education and informed consent. All participants in the pregnancy prevention program must be adequately informed about the risks associated with intrauterine exposure to this teratogen. It should include patients, guardians, physicians, pharmacists, and other health care professionals. The informed consent emphasizes the importance of compliance with program requirements. This education may be accomplished, as you have heard today, using multiple instruments or tools such as labeling -- and we think that in this case the label is already a method that we have used and it's not working -- printed materials, videos, physician counseling, and continuing medical education courses.

The next element to consider is participation. The completeness of participation will definitely have an impact on the program's performance. Complete participation in a pregnancy prevention program is essential because all patients should benefit from the protection provided by a comprehensive PPP. Registration of program participants will provide a denominator and even more important than that is the fact that it serves as a platform for other interventions directed to assure compliance with pregnancy prevention practices.

A third element considered in this design is the tracking of pregnancy exposure and fetal outcomes, including pregnancy registry, patient surveys, and other sources of information of pregnancy exposures independent from the program itself.

The most important measurement of a success of the pregnancy prevention program is the number of exposed pregnancies among program participants. Effective tracking is required to obtain accurate numbers of pregnancy exposures. The tracking of pregnancy exposures and outcomes may be accomplished by the maintenance of a pregnancy registry, meaning a pregnancy exposure and outcomes tracking system to document and follow pregnancy exposures and record pregnancy and fetal outcomes.

It may also be accomplished by surveying

pregnancy prevention participants such as it occurs in the Slone Survey.

And it may also be accomplished by the acquisition of data from external sources. These data sources represent a supplemental source of pregnancy exposures and outcomes independent from the pregnancy prevention mechanism. An example of this is the data that can be acquired through the Organization of Teratogen Information Services, which is a toll-free service organization, as you heard early on today.

The fourth element to be considered is compliance. You may recall from this morning those worrisome numbers on compliance with core pregnancy prevention program components reported from the Slone study. You may also remember the amazing regulatory history of Accutane, the countless Dear Doctor letters, label changes, patient brochures and intensive educational efforts by the sponsor. Noncompliance is still documented in spite of all the company efforts to communicate the risk of teratogenicity through education alone. They have tried and we have tried very hard for 18 years, but without success. In this case, education alone has not done the job.

Optimal compliance with pregnancy prevention practices is essential to minimize the risk of pregnancy

exposure to Accutane. Incentives for compliance need to be engineered into the program to ensure that FDA public health goals are met. A way to assure compliance is by creating a linkage between a negative pregnancy test and other core pregnancy prevention program elements, such as adequate use of contraception and the dispensing of the Accutane.

An example of such linkage is the case in which the physician documents a negative test, the pharmacist verifies that a negative pregnancy test has been documented, and then the drug is dispensed. And several examples of that have been presented already today.

Finally, we must take into consideration the potential benefit derived from restricted drug distribution to pharmacies. A restricted distribution to pharmacies provides an additional safeguard against inappropriate use and dispensing. It imposes restrictions on pharmacies to ensure compliance with dispensing constraints. Pharmacies would have to be registered and comply with dispensing requirements to be authorized to carry and dispense Accutane.

This was just a discussion of the elements that we will be using in the different designs. We have already discussed the goals. We have already discussed the elements. Now, let's discuss the various designs of a

pregnancy prevention program using these building blocks, always keeping in mind that the fundamental objective of this process is to design a program that will meet our public health objectives.

The first design includes two of the five elements that we just mentioned. These are education and informed consent and some of the elements necessary for tracking pregnancy exposure. This design is our representation of the sponsor's proposal.

Design number 1 includes education and informed consent. I must say that the sponsor has done a terrific job enhancing the educational component of the Accutane pregnancy prevention program. These enhancements included major improvements to the PPP kit, labeling changes. It also includes a proposal to improve tracking through the Slone. The sponsor will continue tracking pregnancy exposures and will enhance data collection instruments employed to obtain the data from patients who elect to contact Roche directly to report a pregnancy exposure.

To attempt to improve compliance with pregnancy testing, as you have heard, the sponsor has offered -- and is already doing it -- to supply urine pregnancy tests to all patients during all treatment months.

The advantages of this design are that it intensifies the efforts to educate. It stresses the

importance of pregnancy testing and adequate contraception. Patient urine pregnancy test kits may increase the frequency of testing before and during therapy and may result in earlier identification of pregnancies, reducing this way the length of in utero exposure to Accutane.

However, design number 1 meets only part of our monitoring goal by providing some data on pregnancy exposure and outcomes via surveys and the pregnancy exposure tracking system.

Participation in the program by patients and physicians is still voluntary. Compliance with program components is voluntary and incompletely measured, and measurement of pregnancy exposures and outcomes is still limited.

There's no documentation of program compliance such as negative pregnancy tests prior to Accutane dispensing. Non-participants can still prescribe without constraints. It does not address the other elements of compliance such as the adequate use of contraception.

Design number 2. We have now added patient registration and tracking of pregnancy exposures and outcomes via external, independent data sources. I just want to highlight that there are other effective programs in which the testing is linked to the dispensing and clozapine is an example.

In this case, all patients are required to registered at a data center. The tracking of pregnancy exposures will still involve the Slone Survey and the sponsor's records of pregnancy exposures. In addition, the tracking of pregnancy exposures will be enhanced by the addition of independent data sources.

The design number 2 meets part of the monitoring goal by requiring universal patient registration. This design provides us with a denominator. No more assumptions are needed, no more estimates. The tracking of the pregnancy exposures and outcomes has been enhanced by the addition to the Slone Survey and to spontaneous case reports other external data sources which could help us identify further cases of pregnancy exposure not detected by the pregnancy prevention program in place.

The advantages of this design are that the risk management goals are not met because pregnant women could still be started on Accutane. Women could become pregnant during treatment with Accutane. The monitoring is still incomplete. It involves the creation of a data center to handle patient registration, and besides, it puts a burden on female patients who will need to be registered.

Design 3. To optimize compliance with pregnancy testing, this design includes the additional feature of a link between documentation of a negative

pregnancy test in the database and the prescription dispensed. It retains all the elements from the previous designs with these added features.

To optimize compliance, we introduced the concept of a real-time linkage between pregnancy test results and dispensing. The no-test/no-drug policy. The implication is that all physicians wanting to prescribe Accutane will need to register in order to gain access to a central database to document pregnancy test results. The pharmacist on the other end will confirm that a negative pregnancy test has been documented before dispensing a prescription for Accutane.

So, the process will begin here with patients and physicians registering. This will give physicians an access to patient information and they are going to document the negative pregnancy test which the pharmacy will verify later on.

This design meets our first goal. It provides a mechanism to confirm that female patients are not pregnant prior to dispensing of Accutane. It provides for real-time intervention prior to dispensing. Recording of pregnancy status is now unambiguous and it's documented. It meets part of our second goal because it prevents pregnancy exposure by pregnancy testing. It meets our third goal because of the monitoring of pregnancy exposures

becomes comprehensive by the linkage mechanism. We must remember that the average duration of Accutane treatment is from 4 to 5 months, not a long time, but a high risk period of time for an unwanted pregnancy.

The advantages of this design are that it avoids pregnancy exposure by testing. However, compliance with effective contraception is not being considered. There is need to create a data center to handle registration as in the previous design and for pregnancy test documentation. It also results in a burden for physicians and patients who now are required to registered. Also, pharmacies are now required to validate a negative pregnancy status before dispensing.

The next design is number 4. We have now expanded the linkage between compliance with pregnancy prevention practices to include documentation of patients' reports of compliance with two effective methods of contraception.

All the elements from the previous design are maintained, and to optimize compliance that no one gets a prescription for Accutane unless all pregnancy prevention elements have been completed, this is by documenting a negative pregnancy test and by documentation of reports of compliance with two effective methods of contraception. It creates the scenario for contraceptive use counseling.

The advantages of design number 4 are that it avoids pregnancy exposure two ways: by checking for a pregnancy and by documenting patients' reports of compliance with two effective methods of contraception every single time a prescription is about to be issued. It creates the scenario as well for contraceptive use counseling, and all our public health goals are met with this option.

Some of the disadvantages of this design include that there is a need to create a database and it creates a burden on patients, physicians, and pharmacies because of the restrictions imposed.

Design number 5, our final design, includes the additional safeguard of limiting the distribution of the drug exclusively to pharmacies complying with all the verification requirements we have already described. All the elements from the previous design remain. It adds restricted distribution to pharmacies imposing restrictions on pharmacies. In order to assure compliance with linked dispensing constraints, pharmacists will have trained, registered, and authorized before they would be allowed to dispense prescriptions for Accutane.

Advantages of design number 5 is that all goals are met, and it adds an additional safeguard against the inappropriate use and dispensing of Accutane.

However, there's again a need to create a centralized database, and it burdens physicians, patients, and pharmacies. And now it requires pharmacies to be registered and certified. It restricts distribution of Accutane and it may decrease access to the drug and also encourages alternate sourcing.

Which goals are met by each design?

In design number 1, although there is some monitoring, it is still not sufficient to reassure us that the two other goals are met.

Design number 2 improves somewhat the monitoring goal. However, the only real value added is that now we definitely know our denominator but it still relies of voluntary reporting of pregnancy exposures.

The engineering of a real-time linkage between pregnancy test results and the dispensing of Accutane now identifies pregnant women and women at risk before they get the drug, thus fulfilling the first goal that no one starts Accutane if pregnant and the second goal, that if pregnancy occurs in the time elapsed between office visits, it will be identified as early as possible. Finally, monitoring is as complete as it can get in this situation.

The addition of the other requirement to check for contraceptive use status increases the opportunities to identify patients at risk and provides the opportunity to

intervene, counsel, and correct the problems identified by the physician. All goals are met by design number 4.

Design number 5 reiterates the importance of compliance with all pregnancy prevention program components and it also meets all our public health goals.

The sponsor's proposal will not achieve the three core goals of a pregnancy prevention program. Time has proven that education alone has not been sufficient to modify patients' and prescribers' behavior. Other program designs provide an opportunity to achieve FDA's public health goals. However, these other alternatives do not come without additional burdens.

We're asking you to help us answer the question, how should we balance the achievement of this important public health goals with the burdens imposed by the various designs I just described?

DR. BERGFELD: Thank you.

I'll entertain very brief questions of clarification at this point before we break for 15 minutes, if there are any. Dr. Rosenberg.

DR. ROSENBERG: I have a question. I don't know whom to ask, perhaps Dr. Greene or someone else. Suppose that instead of monthly visits or weekly visits, there were a daily dose attached to a self-pregnancy test. Would there be any utility to doing it every day or every

other day or every third day?

DR. GREENE: Well, as Dr. Lammer described, the real risk is associated with exposure after about 15 days after fertilization. So, yes, in theory if you did a pregnancy test every single day, you would recognize pregnancy quicker than if you did it once a month. As a practical matter, I think that gets rather intrusive, and I'm not sure it's workable.

DR. BERGFELD: Any other questions? Yes.

DR. MALONE: In the clozapine program, are pharmacies registered or not registered?

DR. BERGFELD: Dr. Vega, can you answer that?

DR. VEGA: Dr. Bull, do you want to address that question?

DR. GRAHAM: David Graham. I'm with OPDRA.

When the program was initially instituted, the pharmacies were registered. Eventually that was changed, but what happens is the drug is only sort of basically authorized for clearance and then dispensing, if you will, by the central data house that records the performance and the normal result of the white blood cell count. So, in essence, you restrict the distribution of the drug. Pharmacies are able to now dispense it, but only after clearance using a coding system that sort of ensures that the test has been done and the result is normal.

DR. BERGFELD: Yes, Dr. Malone.

DR. MALONE: So, initially when pharmacies had to be registered, what percent of them did not get registered? Does anybody know that?

DR. GRAHAM: I think initially all pharmacies that distributed the drug were registered. I don't know what the percentage was of pharmacies that didn't register, but there was I believe public outcry from pharmacy associations being denied the opportunity to dispense the drug. So, this alternate system was devised.

DR. BERGFELD: Any other questions, clarification for Dr. Vega's presentation? Dr. Vega, any other statements?

DR. VEGA: No.

DR. BERGFELD: Well, we will break for 15 minutes. We will reassemble here at, it looks like, 4:35 and carry on with the rest of today's activities.

(Recess.)

DR. BERGFELD: If everyone could take their seat, we could then get on with what we have to accomplish for the rest of the afternoon.

As chair, I've made a decision to invite to the podium Jay Kaminski, who is the Chief Executive Director of Celgene, and he will tell us about the STEPS program and the actual compliance of the pharmacists in that program.

MR. KAMINSKI: Thank you. I'm Jay Kaminski. I'm in charge of commercial operations with Celgene Corporation. We are the company that distributes thalidomide through the STEPS program.

Currently through our program, it is a mandatory registration process with physicians, pharmacies, and patients. All patients are required to do an informed consent and a mandatory survey through Boston University. The patients are registered at the pharmacy. All pharmacies must be registered with Celgene in order to receive Thalomid and stock Thalomid. They must record all dispenses and dispense information with Celgene Corporation prior to giving out the drug. If they do not, we withhold shipments of future product until they do become compliant in giving us dispense information.

Currently we have undertaken this process for education at the pharmacy level, at the physician level, and at the patient level to avoid fetal exposure.

DR. BERGFELD: Can you give us an idea on the compliance and how many times you've held back the shipment, if that is the punishment if you don't comply?

MR. KAMINSKI: The biggest issue we've come into after two years of experience with the program is the level of work that the pharmacies have to do, being managed care and patients and education, as well as distribution.

So, we've had to place some outbound calls to get prescription information prior to releasing orders several times, not terribly many, but we certainly have had to do that.

DR. BERGFELD: So, you would deem your program successful at this point or just still in the developing phase?

MR. KAMINSKI: I think what we took upon ourselves, after about a year on the marketplace, is to reevaluate the program. We are in the process of enhancing the program and hope to be rolling out an enhancement, if you will, in the fourth quarter of this year utilizing some very interesting technology and really to improve the program.

DR. BERGFELD: Would you mind staying there until I ask the committee if they have any questions specific of you? Yes, Dr. Woodcock.

DR. WOODCOCK: Could you comment on how many pharmacies are enrolled in this program?

MR. KAMINSKI: Sure. We currently have about 10,500 pharmacies enrolled in the program. Approximately 2,000 to 2,500 pharmacies dispense on a regular basis. They tend to be self-selecting pharmacies that distribute specialty products. We roughly have about 9,000 physicians who are registered to prescribe in our STEPS program.

DR. BERGFELD: Yes, Dr. King.

DR. KING: I again come back to an issue. How do you know that other sources such as non-U.S. sources or even on the Internet are having thalidomide coming into the system here that you can't track?

MR. KAMINSKI: I think that is an ongoing problem for manufacturers in the United States. We also, like our colleagues Roche, monitor that. We haven't seen any problems yet, although we do monitor it very closely. We have had reports, in particular, from two countries, Brazil and Mexico. Those countries do distribute thalidomide on their own in that marketplace.

DR. BERGFELD: Any other questions?

(No response.)

DR. BERGFELD: Thank you very much.

The agenda notes at this point in time we are to go into a committee discussion. We've had some lengthy discussion that was a little bit early right after lunch, and I'm wondering if there are any other questions that the committee might have in general of FDA, Roche, or others. Yes, Dr. Greene?

DR. GREENE: I have one question, and I'm not sure who the right person to address it is, possibly Dr. Mitchell. We've heard today that 85 percent of prescriptions are written by dermatologists. Do we have

any knowledge about what percentage of inadvertent pregnancy exposures occur as a result from prescriptions written by dermatologists versus non-dermatologists? You know, the Willy Sutton principle.

DR. MITCHELL: We don't have that direct information available. We have some indirect information which suggests that compliance within women who enroll in the survey is better among those who have a dermatologist as the prescriber than among those who don't.

DR. GREENE: But no real numbers?

DR. MITCHELL: No, I don't.

DR. ELLISON: We have the numbers based on an analysis of all spontaneous reports. Basically in a nutshell, because of who reports -- sometimes it's the patient, sometimes it's another provider that will actually report the pregnancy -- here are a fair number of unknowns in this. Of the ones that we know, it's a very similar pattern.

Now, the problem is the percentages are given of the total which includes the 37 percent unknown. I think you can see that of the ones we know, basically the dermatologists are indeed the majority, as they are the majority of the scripts.

DR. BERGFELD: Yes, Dr. Lammer.

DR. LAMMER: Dr. Greene, my experience is, with

pretty complete data, about 90 percent of the malformed babies and pregnancies that we've identified, the prescriber was a dermatologist, and that's pretty close to the relative proportion that I think Roche has quoted before. So, among the pregnancies at least that we've tracked, it's pretty similar to who seems to be prescribing the drug.

DR. BERGFELD: Dr. Rosenberg.

DR. ROSENBERG: The question is not of education but information when you need it. I ask Roche, do the blister packs have an 800 number on them? Do they have a web address on them? Is the 800 number 24/7, and is the web page very helpful to somebody who is worried in the middle of the night?

MS. LEACH: We have a FaceFacts web site which is non-branded and so, therefore, does not give Accutane information. However, the toll-free numbers for the Accutane information line and for the confidential counseling line are both 24 hours a day, 7 days a week. The usual reason why people call the information line, that we put into place recently, has been on the forms of contraception they should be using.

DR. BERGFELD: Thank you.

Dr. Kodish?

DR. KODISH: The literature on adherence to

oral medication in adolescents with leukemia suggested about 10 to 40 percent of adolescents with a life-threatening disease will not take their 6-MP, 6-mercaptopurine.

My question is for the FDA, perhaps Dr. Vega or whoever at the agency would be most appropriate. Has the issue of mandating parenteral contraception come up in your thoughts about the risk-benefit analysis, and if so, what were the thoughts around that?

DR. VEGA: No, we haven't discussed that specific issue.

DR. BERGFELD: Dr. Abel?

DR. ABEL: Regarding the types of contraception, in this draft to the prescriber for the targeted pregnancy prevention program, when they talk about the types of contraception, could it be more explicitly defined that there must be a primary that is a hormonal type and a secondary which is not? Otherwise, people might ask, well, are two barrier methods okay. Maybe that should be spelled out. Maybe it is in the patient information. I don't know.

MS. LEACH: In the best practices for prescribers, there's a list and a rather lengthy explanation of primary and secondary. It's also in the patient contraception and it's part of the informed

consent.

DR. ABEL: Good.

DR. BERGFELD: Dr. Malone?

DR. MALONE: I just have a comment or question about the time period for monitoring for pregnancy. It would seem that something like 2 weeks is kind of the window if you look at the sensitivity of the test or the exposure to drug, 2 weeks or less. But it seems that most people are talking about monthly monitoring. So, I'm just wondering about that difference between 1 to 2 weeks for the risk, but monthly monitoring.

DR. BERGFELD: Is there a response from FDA or Roche?

DR. VEGA: By monitoring monthly, the woman comes to the office and gets a test done. In a period of 1 month, if she was not pregnant at that moment, then a 1-month period will pass by before she gets her next menstrual period, and then at the second or third day of her menstrual period, she's going to get the second pregnancy testing. That's at the beginning of therapy, that you get two pregnancy testings. So, that will presume that you have just 2 weeks of exposure after that window of time if you check during the second or third day of the menstrual right before you started the treatment.

DR. BERGFELD: Dr. Mills?

DR. MILLS: I'd like to just comment on how the more active proposals by the FDA would help to resolve some of the problems identified by the Slone study. For example, the Slone people reported that in 14 percent of the pregnancies, the women were pregnant before they started taking the medication. 12 additional percent occurred when the women started taking the medication before the menstrual period, both of which would be curtailed considerably by the proposal requiring a negative pregnancy test before the drug could be prescribed.

Secondly, the proposals that ensure compliance with contraceptive practices would be very useful because in the Slone data, less than 50 percent of the subjects actually used two methods of contraception. If you notice, some of the women were using the rhythm method, which we all know is not a terribly good method of contraception.

What is not so clear in terms of a problem that would be corrected by the FDA proposals is that a substantial number of the women had problems because of unexpected events. 11 percent of the women said they were going to be abstinent and then changed their minds, and 34 percent didn't use contraception at the actual date of intercourse. So, you have 45 percent of the women who are unexpected events in terms of the pregnancies.

I wonder if we could have some discussion of

the question of postcoital contraception because that whole 45 percent of pregnancies, those who neglect to abstain, we might say, or who don't use contraceptives for that particular episode might benefit by postcoital contraception. I don't know if that's in anybody's plans at the FDA.

DR. BERGFELD: Does the FDA want to respond to that?

DR. VEGA: Because we have been thinking about this whole process, these designs in general terms, right now we can get into the specifics, but I can tell you that that's part of the STEPS program, for example, the emergency contraceptive. We do have it on our radar screen, and the reason why we haven't presented it here is because we don't to get into the specific details of these programs. But definitely that should be a feature of any of these designs.

DR. BERGFELD: Can I say that I did hear that Roche presented the emergency contraceptive program that has already been introduced into their informational pieces. Has that been reviewed by the FDA and approved?

DR. WILKIN: I'm not sure that we have seen every single piece of the new program.

MS. LEACH: In fact, in the orange package that you received is the final draft of the piece.

Pregnancy prevention changes are reviewed by the FDA after they're first launched. It's only when you're bringing pieces out that are connected to an approval of an NDA that they get reviewed in advance.

DR. BERGFELD: I'm sorry. You'll have to clarify that again. You're here today because there is a proposed pregnancy problem with the drug, and you're proposing some changes in your educational material and you've not shown those to the FDA. Is that what you've said?

MS. LEACH: Yes. Actually we submitted them to the FDA in March of 1999.

DR. BERGFELD: But they don't have to approve them, but they've seen them and read them.

MS. LEACH: They don't have to approve of them. Obviously, we would love for the FDA to make an approval statement, but since it's not in connection with a new NDA, it's not part of the regulation.

DR. BERGFELD: Dr. Wilkin, do you want to respond to that?

DR. WILKIN: Well, I haven't looked at everything in the brown paper wrapper here that I found on my setting here today. But what you are describing is that we have seen everything that is in the -- yes. She's claiming that we've seen everything that's in this package.

DR. BERGFELD: Yes, Dr. Anderson.

DR. JENNIFER ANDERSON: When I asked a question earlier about one aspect of it, you said that Dr. Mitchell had not yet reviewed it, which is paradoxical to me.

MS. LEACH: No. We submitted it to the agency in March of 1999. Dr. Mitchell wishes to go over the final wording. He has seen this also.

DR. WILKIN: Just a point of clarification. Was this submitted to DDMAC or to the division?

MS. HOLLAND: My name is Betty Holland. I'm with Hoffmann-LaRoche. The information about the proposed changes was included in the package we submitted to you, to the reviewing division, in March of 1999. The materials have not yet been submitted to DDMAC for their review.

DR. BERGFELD: Thank you very much.

Dr. Wilkin, may I ask you a question about it? Because of the issue of pregnancy and the attempt to stop birth defects and thus pregnancies, will you be reviewing this with some great interest?

DR. WILKIN: Well, if it's the material that we've seen actually, then we have. My comment was that I have not reviewed the material that is physically in this brown wrapper today to know whether we have seen it and reviewed it within the division.

DR. BERGFELD: Well, it seems that

clarification and focus on this might be appropriate.

Any other comments by the committee before we move into the questions that are posed for the committee? Yes, Dr. Abel?

DR. ABEL: What is in the brown wrapper? New material then, fairly new or revised that we have today?

MS. HOLLAND: The materials that you have in the brown wrapper are the final drafts of the pregnancy prevention program materials that are being developed that will be distributed, as Ms. Leach indicated in her presentation. These are to be going out in the September-October time frame.

DR. BERGFELD: Thank you.

Dr. Levin?

MR. LEVIN: I just want to pursue the emergency contraception issue because it seems to me to be really helpful that a 1-800 number would actually have to refer people to resources where they could get emergency contraception, I mean, more than just say it's something you can do, see your doctor. I don't think that's helpful enough. It would be much more helpful to actually have resources that people could be directly referred to.

DR. BERGFELD: Thank you.

Dr. Mills.

DR. MILLS: Right, or how about just providing

that to people so that they'd have it there when they needed it?

MS. LEACH: Information on emergency contraception is included in the Best Practices. It's also included in the Preventing Pregnancy booklet, and the advice is for patients to call 1-800 Not Too Late, which is an emergency contraception counseling line.

DR. BERGFELD: Any other questions that the committee might have of any of the participants? Yes, Dr. Moore?

DR. MOORE: Are we going to discuss each of these options separately or if we have questions about --

DR. BERGFELD: We're going to discuss the questions that the FDA has posed to us that you should have in the handout.

DR. MOORE: The five designs?

DR. BERGFELD: Yes. They're going to be presented by Dr. Bull.

DR. MOORE: Okay, thank you. I'll hold till then.

DR. BERGFELD: Are we ready for the presentation? If you please.

DR. BULL: It might be helpful, if it was a point of clarification on one of the designs, if we take that question now.

DR. BERGFELD: All right. Is there a point of clarification?

DR. MOORE: Not really.

DR. BERGFELD: If you'd like to proceed then with the questions.

DR. BULL: I think we've heard today several clear messages, the first being that Accutane is a drug that is known to be highly efficacious in the treatment of cystic nodular acne. The other that has come out I think clearly is that there are other models that do evidence mechanisms by which drugs can be monitored to ensure their safe use.

Our goal was to lay out for you all our concerns regarding the continued presence of pregnancy exposures associated with the use of the drug and to raise questions as to the sufficiency of the program as it's currently laid out.

Our questions to the committee. Question 1. And all of these are considerations that we see framed from a risk management perspective. The agency has outlined and presented to you three goals for a successful risk management program for Accutane, the first being no one should begin Accutane therapy if pregnant; number two, no pregnancies should occur while on Accutane therapy; and the third, implementation of a monitoring program to ensure

that the above two goals are met.

Does the committee agree with these goals?

DR. BERGFELD: I'd like you to read all the questions and then I'll take them up individually.

DR. BULL: Are there others that you would recommend as goals?

Question 2. Of the five designs presented by FDA, which is the most likely to achieve the stated goals while balancing the associated burdens? Please discuss why you chose this design.

Question 3. How can the FDA best monitor the impact of the pregnancy prevention program? Possible options include: number one, registration of additional parties, such as patients or pharmacists; number two, obtaining data on compliance with the program; number three, utilizing an external monitoring program to assess pregnancy exposures and outcomes.

DR. BERGFELD: Thank you very much.

What I'd like to do is to proceed with the question 1 first, but then I would also like to state that the voting members will be the voters. However, the discussants can also include the nonvoting members.

So, we'll first begin with the discussion, and this is on question 1 and I'll repeat it. The agency has outlined three goals for a successful risk management

program for Accutane. One, no one should begin Accutane therapy if pregnant. Two, no pregnancies should occur while on Accutane therapy. Three, implementation of a monitoring program to ensure the above goals are met. The first part of the question is, does the committee agree with these goals? And I'll entertain any discussants. Yes, Dr. Branch.

DR. BRANCH: Sort of setting a stage from a perspective of public health policy, it seems to me that there are two major drugs that have been very, very clearly and unequivocally associated with fetal abnormalities. There's thalidomide and there's the drug that we're considering now. It seems to me that the information base behind that for the retinoic acid story is unequivocal and that the same set of considerations should take place. We are in a position to prevent fetal abnormalities in this country. It's a question of how to do it, but in terms of a starting point, I think we should have a level playing field for drugs of equal teratogenic potential. So, that's an opinion.

DR. BERGFELD: So, your opinion is yes, you agree with these goals.

DR. BRANCH: I agree with these goals.

DR. BERGFELD: Thank you.

Dr. Rosenberg.

DR. ROSENBERG: As I read this, everyone must agree with goal 1, no one should begin Accutane therapy if pregnant, and 2, that no pregnancy should occur while on Accutane therapy. But it's not clear to me how implementation of a monitoring program will ensure that those goals are met. It would tell you if they were not met and upset you, but it seems to me that if I vote for statement number 3, I'm not sure I'm going to get 1 and 2.

DR. BERGFELD: Dr. Holmboe?

DR. HOLMBOE: I think your comments are very cogent. I do agree with all three goals.

I'm a little concerned that we haven't addressed some of the other aspects that may get to what Dr. Rosenberg has brought up. Again, that gets back to the informed consent process, the type of information that's going to be given to them, again qualitative versus quantitative. Although we can do this monitoring, we really haven't built anything into this monitoring system to find out if that process that occurs in the office, particularly enough among nurse or physician and patient is effective. So, we may be developing an awful lot of materials that may be quite voluminous and yet not know if the patient who is leaving that office has the desired and needed knowledge to be most successful in avoiding pregnancy.

DR. BERGFELD: My summary of what you said is that you agree with 1 and 2 goals and 3 maybe. Is that correct? Depending on descriptions of the educational process.

DR. HOLMBOE: No. I agree with the concept of a monitoring program. I'm just concerned that we may not be monitoring all the processes that need to be in order to be successful to meet the goals.

DR. BERGFELD: Any other responses? Yes, Dr. Anderson.

DR. JENNIFER ANDERSON: I share some of Dr. Rosenberg's concerns. Actually I feel it's very difficult to vote on these three as a package.

DR. BERGFELD: You are allowed to split them out if you would like to.

DR. JENNIFER ANDERSON: You are?

DR. BERGFELD: Yes. If we can get unanimous decision on 1 or 2 and then discuss the third one, that would be appropriate.

DR. JENNIFER ANDERSON: Well, on the second one, I know that's the ideal, but as a goal I think it would be more appropriate to say that a very minimal number of pregnancies should occur. Absolute zero is not possible unless nobody takes the drug.

DR. BERGFELD: Dr. Branch and then Dr. King.

DR. BRANCH: We're talking about goals not implementation. It seems to me that a goal is something you're striving for, and then we can discuss how you implement it. But as a goal, it seems to me these are very meritorious and pretty clear-cut. I don't think how you get to them is so clear cut. I'll put on the table that this is what we should start with.

DR. BERGFELD: Dr. King?

DR. KING: I'd like to vote on the first two and defer the number 3. I think the goal of zero tolerance versus acceptable risk is two different things. Our goal should be 1 and 2. I think in the case of cigarettes or other kinds of things where the incidence rate may not be any higher, I think really you're talking about zero tolerance versus acceptable risk. So, I think that I'd like to vote for 1 and 2 and talk about number 3.

DR. BERGFELD: I'd like to come back to you to have you put that on the table as a proposal, but I need to hear from a few other people. Dr. Tan, I heard you and saw you shaking your head.

DR. TAN: I agree that we should vote on number 1 and 2. There's clear consensus there. For number 3, we need to talk about how to achieve those goals.

DR. BERGFELD: Thank you.

Dr. Woodcock?

DR. WOODCOCK: If I just may provide a point of clarification on goal number 3. Perhaps this isn't worded exactly the way that people can understand what we mean by this. But in any risk management program, if you do not have adequate metrics to determine what your achievement rate is, then you do not know whether your interventions are actually effective or not.

DR. ROSENBERG: Do you mean to say to "see if" rather than "ensure that"?

DR. MURPHY: "Assess."

DR. WOODCOCK: To measure the progress, or whatever, is what we mean. Yes.

DR. BERGFELD: Could you restate number 3 then?

DR. WOODCOCK: Implementation of a monitoring program to assess progress toward the above goals.

DR. BERGFELD: That does improve it. Anything else?

DR. WINOKUR: Andy Winokur from U. Conn.

I was going to chime in. I also agree with 1 and 2. In spirit with 3, I think the education program that we've heard about from Roche is terrific, but I also have a sense and agree I think with the FDA presentation that something more and more formal to really address the worrisome aspect of the exposure is needed. So, I think the third point takes us to discuss the specifics of how to

put that part in place.

DR. BERGFELD: Thank you.

Dr. Dianne Murphy and then Dr. Cindy Moore.

DR. MURPHY: I was simply trying to point out that that should be assessed. That was all.

DR. BERGFELD: Thank you.

Dr. Moore?

DR. MOORE: I understand changing that to "assess" and I agree with it, but not in the absence of saying that there should be implementation of a program to ensure the goals and that would include a monitoring component to assess the progress.

DR. MURPHY: Again, I think our goal for the third goal is that we can't improve something if we don't know how it's performing. So, we misstated. We are trying to say we want to have a monitoring program where we would assess the success of the activities, whatever they are, and that we would then look at how successful or unsuccessful it was and have to try to address those issues to ensure that we reached our first two goals.

DR. BERGFELD: And I gather that someone will put that sentence together somewhere.

Yes, Dr. Greenhill.

DR. GREENHILL: Dr. Greenhill from Columbia University.

I agree completely with goals 1 and 2, and as other people have said, the problem that often one would have with number 3 is that it's stated in a very different form than the first two goals. For example, what are we monitoring? Are we monitoring the number of pregnancies? Are we monitoring whether the contraception program is effective, whether patients are using two different methods, one involving a hormone? I think that needs to be stated for it to be put in as a goal.

I would like the goal of monitoring that would detect any possible pregnancies that would occur. That would be a goal, not hoping with the number 0, but we have all the cases of exposure. So, the goal in my mind would be an accurate determination of the denominator. It's a very vaguely worded phrase, so it might include the behavior of the patients or it might not. So, I think some discussion about the contraception methods could come in.

DR. BERGFELD: Would you restate what you'd like that third line to read?

DR. GREENHILL: The goal would be a highly sensitive monitoring program that would give a completely accurate denominator of exposure to determine if a pregnancy occurred. Ideally it would also give information on the types of contraception used in all women exposed.

DR. BERGFELD: Thank you very much.

Dr. Abel, then Dr. Anderson.

DR. ABEL: I'm not sure that monitoring is going to necessarily accomplish and all the qualifications of monitoring are going to accomplish 1 and 2. I would suggest maybe another rewording or possible use of interventions which might include counseling, education, in addition to some monitoring. To restrict it to monitoring for number 3 to accomplish 1 and 2, I'm not sure that's going to ensure that the goals are met.

DR. BERGFELD: Can you give us a line statement on number 3 then, your proposal as a sentence?

DR. ABEL: I'll have to think about it, but I would substitute "interventions" rather than "monitoring." Interventions to include monitoring, but it might also be counseling. It might also be this behavioral research that Roche referred to. There may be other types of interventions to ensure that these goals are met besides strict monitoring.

DR. BERGFELD: Thank you.

Dr. Anderson and then Dr. Levin.

DR. GLORIA ANDERSON: I think she has said essentially what I was going to say. I think the problem here is that when one sets goals, then one has to develop and implement a program to ensure that the goals are achieved. And the monitoring becomes evaluation of the

extent to which they are achieved. So, I think there's a different 3 that needs to be here, and then the monitoring is the evaluation.

DR. BERGFELD: Dr. Levin?

MR. LEVIN: I guess I'm a little confused. It may not be well stated or as well stated as it could be, but I thought this was sort of basic, that if you're going to set goals, you have to have metrics to decide whether you're meeting the goals or not. I don't think this is a place to spell out all the components of what you want to do, and maybe "monitoring" is a bad word. But this seems to me it's useless to set 1 and 2 without a metric, otherwise we're wasting our time and somebody will tell us we've met them and somebody will say, well, you didn't meet them and we'll never know.

So, I don't know how it has to be stated, but it seems to me 3 is integral to 1 and 2. If you don't do 3, don't bother to do 1 and 2 would be my opinion.

DR. BERGFELD: I think that's the general assessment of the whole committee that they need to have some evaluation statements present in the three goals.

Dr. Tan?

DR. TAN: Yes. I just want to say that it's good to have a monitoring system, but I think more importantly you have to find out what went wrong, what

happened once you see a pregnancy. Maybe it's useful to set up a database to track that.

DR. BERGFELD: This proposal that has gone up now is the FDA's proposal for our substitution for item 3. Do you want to read that, Dr. Woodcock?

DR. WOODCOCK: Right. This is the evaluation piece to tell whether or not progress has been made toward goals 1 and 2, and it's implementation of a program -- we'll leave out "monitoring" for now -- to assess the progress toward the above goals. And what that program would do is know the number of exposed individuals and the number of individuals who became pregnant, and that would provide for the epidemiologic investigation of what went wrong, as you said, in those. But the basic concept is right now we don't know the numbers and we've spent part of the day discussing the numbers. If we don't know the numbers now and we implement a risk management program, we won't know whether it worked or not. That's sort of the basic point we were trying to make. So, in order to know whether we have made progress toward 1 and 2, we have to have some sort of evaluation piece. That was strictly our point.

These goals did not include any elements of the risk management program itself, the specifics. These are simply the goals.

DR. BERGFELD: Are there any other points that need to be discussed before we call the question? We have heard from probably one-half of the committee, nonvoting and voting members. Are there others who wish to support or not the three goals that are presented? Dr. King?

DR. KING: I think I'm back to the same issue. I think everybody will vote on 1 and 2 affirmatively, but I just wonder if we should defer it to question 2 because you're going to come then and ask the next question. Of the five designs presented by FDA, which is most likely to achieve it? Here we are talking about minutia in a broad goal, which I believe in motherhood and apple pie, and then you're going to get down to the down and dirty in the next question. So, I recommend we table number 3 goal here and come back to it and say, sure, we believe you need to have a monitoring system, and we will address the specific issue in question number 2, which the FDA is asking us.

We've done this before. The answer is no, not now. I mean, manana doesn't mean tomorrow, it just means not now. So, I vote for manana for question 3.

(Laughter.)

DR. BERGFELD: A couple things. You've put two proposals on the table: one to vote for 1 and 2, and the second is to table 3.

DR. KING: Until question 2 is considered.

DR. BERGFELD: Are there any other discussants or a second? I'm going to take that as a motion. A second to that motion? Dr. Greene?

DR. GREENE: I'd just like to make a comment. Whatever we decide on number 2, we're going to need some sort of a program to assess progress towards these goals. So, I would not like to see deferment of this question. I think we can vote on it straightaway regardless of what we decide about question 2.

DR. BERGFELD: Dr. Rosenberg, you were motioning.

DR. ROSENBERG: I was seconding Lloyd's motion. I don't think we should spend any more time on this. It goes without saying we have to know whether we're succeeding toward getting a goal, but that in itself is not a goal actually. But anyway, it really doesn't matter, I don't think. I was just afraid at the beginning that it was phrased so that it made it sound like the monitoring would achieve the goal which, of course, it doesn't.

DR. BERGFELD: So, your motion is not seconded. So, we might call for a motion on the whole, which are the three different goals that have been proposed. Any other discussion regarding these three goals?

(No response.)

DR. BERGFELD: Seeing none, then I will ask the

voters to raise your hand if you are voting yea at this point in time. All those in favor?

DR. JENNIFER ANDERSON: What is the exact wording?

DR. BERGFELD: The exact wording for 3 will be developed, but the intent is up there.

(A show of hands.)

DR. BERGFELD: It looks like it's unanimous.

Those against, please raise your hand.

(No response.)

DR. BERGFELD: So, it's unanimous.

Are there others that you would recommend, which is the second part of that? I think the discussion would probably answer that. We need not go any further unless someone has other things to comment upon.

Then moving then to question -- yes.

DR. ROSENBERG: I'd like an explicit goal that there be no children born with Accutane-induced birth defects. I'd just like to say it that way. That's not an easy issue. If no pregnancies occur, that's wonderful, but if pregnancies occur, then what? I for one am certainly not about to suggest policy, but I feel strongly that we ought to address that question. And if we had a goal that there be no children born with Accutane-induced birth defects, it would I think change the content of the

discussion.

DR. BERGFELD: Yes.

DR. HOLMBOE: I don't see how we can do that. I think that's equivalent to saying that nobody with Down's syndrome should be born. I think once a pregnancy occurs, that's a personal decision on the part of the parents, and I don't think we're in a position to be making a statement that no children should be born no matter how bad the birth defects might be. I think that's just got to be a personal decision. We have lots of congenital abnormalities in which parents make the conscious decision, despite knowing from ultrasound or other technologies, what the outcome is likely to be. So, I feel pretty strongly that we're not able to do that.

DR. BERGFELD: Dr. Levin, then King, and then Malone. Nothing? Dr. Malone?

DR. MALONE: I was just going to agree with what was just said that the goal as it is is good enough I think.

DR. BERGFELD: Thank you.

Dr. Kodish?

DR. KODISH: Just to make the point that sometimes things are better not said, and I think you achieve what you want with goals 1 and 2.

DR. BERGFELD: Thank you.

Dr. Jones?

DR. JONES: Yes, I'd like a point of order.

DR. BERGFELD: Certainly.

DR. JONES: On the voting consultants that I got through the mail last week, I'm a voting consultant. On the thing that came today, I am not a voting consultant.

DR. BERGFELD: We'll let the Executive Secretary answer that.

MS. TOPPER: You actually happen to be a matter of federal paperwork. Your paperwork was not in time for personnel action to take place. Therefore, you are not able to vote.

(Laughter.)

DR. BERGFELD: Dr. Rosenberg, you wanted to have a closing comment?

DR. ROSENBERG: Could I change that, that there be no children born with Accutane-induced birth defects unless the parents felt that that was their wish?

I just feel that nobody is offering anything except, "sorry, you lost" to people who failed at this game, and I just feel for somebody who all of a sudden says, my goodness, I've been taking Excedrins instead of Ortho-Novums. I just realized. And you do a test and it's positive, and now what? Are we all going to pretend that we wash our hands of this, we ignore it, we tell them,

sorry, kid, you lost? Who is willing to step up to the plate here and say, now what?

DR. BERGFELD: Dr. Anderson, Dr. Jones, Dr. Lammer, and Dr. Bull.

DR. JENNIFER ANDERSON: I agree with Dr. Rosenberg. That's all I want to say. If that's a proposed goal that you're putting out, I second it.

DR. BERGFELD: Dr. Jones?

DR. JONES: And I third it. I think that clearly the risk here is the conception of a fetus or embryo with a birth defect. One way to deal with that from the standpoint of management is a pregnancy prevention program. There's absolutely no question about that. But we've heard today and when you read the literature, it's clear that it doesn't always work. There are clearly many babies that are conceived whose mothers on Accutane that they continue on in their pregnancy. The risk still remains the baby with the birth defect, and we've got to manage that problem. The way that we have been shown that we manage that problem today is through therapeutic abortion, and that is a tragedy. It's not an appropriate way to deal with it, and for those people that elect not to do that, the issue is that they have a child with a birth defect.

So, I think we need, in terms of management of

this risk, to think very seriously. And I must tell you that I believe very strongly in this, that Hoffmann-LaRoche is responsible for the payment of pregnancy termination. I do not think that this should be the pregnant woman herself. I do not think that this should be the taxpayers of this country, and I also believe that Hoffmann-LaRoche should be responsible for paying for the treatment for children who are born with birth defects secondary to exposure to this drug.

I think what you are going in terms of pregnancy prevention programs is fabulous, and that's one management program to deal with the risk. But you've got to recognize that the risk is not pregnancy; the risk is a baby with a birth defect.

DR. BERGFELD: Thank you.

Dr. Lammer?

DR. LAMMER: Well, I think I've said pretty similar things to what Ken just said at previous hearings here, and it really I think is true. The history of what's gone on at these hearings has been that this is an essential drug to be available for dermatology patients. And I've had former members of this committee tell me outside of the hearing room that the morbidity and mortality to the babies that results from having this drug available is an acceptable side effect, if you want to call

it that, of making this drug available.

Yet, through all that time, for these parents who are taking care of these kids and the public, all of us who are also paying for that, there has never been a proposal that if this drug is so essential to have for those patients and if this is a consequence of keeping it available, that there ought to be some mechanism set up that these families are assisted in taking care of these children, many of whom, from Dr. Adams' and my experience, are not going to be able to live independently as adults, and that's the survivors.

DR. BERGFELD: Dr. Greenhill and then Dr. Bull.

DR. GREENHILL: Just a point of information. Is it possible to detect which of the children exposed in utero through amniocentesis have the developmental deviations before delivery?

DR. BERGFELD: Dr. Lammer?

DR. LAMMER: That's an easy one. No.

DR. BERGFELD: Dr. Bull?

DR. BULL: I just had a point of clarification. Is the additional item under discussion an additional recommendation to the goals?

DR. BERGFELD: That's correct. Dr. Rosenberg has proposed an additional goal.

Yes, Dr. Branch.

DR. BRANCH: I come out on the other side of this. I think we're going beyond the purview of this particular review. If we go on record as making this a goal, then there has to be an action that follows it. There has to be something that takes that goal and makes it a reality. What you're doing here is you're going directly into the rights of the mother at that point in time.

I absolutely endorse all you say about it being a tragedy. It is a tragedy for that family. They have a tremendous burden. Therapeutic abortion is a terrible decision. Going ahead is a terrible decision. It's a no-win type situation.

But trying to implement programs that come in at that point of intervention and the limited capacity that we have to actually intervene after the fact, I think this is a public health issue that is dealt with by prevention and is not dealt with appropriately by us going on record after the fact. So, I would vote against it.

DR. BERGFELD: I'd like to ask the FDA at this point in time -- you've heard the comments regarding Dr. Rosenberg's suggestion of an added goal and you've heard many members of the committee speak to this. I would suggest at this point in time we pass on because we're unable to solve this, I'm sure, because of this political/social problem. Is that all right with you?

DR. WOODCOCK: Yes.

DR. BERGFELD: Thank you.

They will take this up, Bill, at another level.

So, I think we'll proceed to question 2. Of the five designs presented by the FDA, which is the most likely to achieve the stated goals while balancing the associated burdens? And the second part, please discuss why you choose this design.

Would there be any commenters on this? We had five different designs that were presented us. Dr. Greene?

DR. GREENE: I'd like to make a generic statement about this first and that is that I view some of what I've heard today with a little bit of alarm. One of the principles of ethics and medicine in the United States is the principle of autonomy. When I hear people say things like presenting evidence that someone is on several methods of contraception, things like requiring injectable contraception, as evanescent of the notion of abstinence may be, nonetheless, there is the issue of autonomy.

If a woman who is fully informed -- I'm not talking about a child or a minor, but if a fully informed adult woman says that she is abstinent and says that, recognizing everything that we've had to say about the risks associated with taking Accutane that she doesn't need and doesn't want contraception, I would have a tough time

telling that adult woman that she can't make that decision for herself, as an obstetrician/gynecologist. So, I view with a little bit of alarm some of what I consider to be rather draconian proposals that would ride roughshod over an adult, competent woman's autonomy.

DR. BERGFELD: Thank you.

Dr. Moore?

DR. MOORE: I have a question about the thalidomide, or the Thalomid, STEPS program. I believe that there is some method in there if the woman does say that she's abstinent or she's chosen that as her method, to agree to that, that she could still get the medication. I wanted to clarify that with FDA.

DR. WOODCOCK: That's correct.

DR. MOORE: It seems to me to be a very specific component of this that perhaps we're getting too much into that.

DR. WOODCOCK: When the STEPS program was instituted, there were quite a few discussions about the issue of autonomy and respect for persons, balancing that against building in system's protections that would support people in not making mistakes. You do have to balance these two things: the principle of protection or whatever versus autonomy. Certainly for people who are abstinent and they practice abstinence, it's obviously a reasonable

contraceptive decision, and that needs to be respected. But you have to balance that in the case, as was said earlier, about where abstinence may be a temporary and fleeting phenomenon.

Probably the availability now in this country of emergency contraception recommendations really does help in dealing with this.

DR. BERGFELD: Dr. Kodish.

DR. KODISH: Just to point out the subtle but important difference between autonomy and respect for persons. I think if you look at the ethics literature, there's a movement away from autonomy as the gold standard and toward respect for persons. It's a little bit more broadly defined.

DR. BERGFELD: Could you define it for us?

DR. KODISH: I think that autonomy is a rights-based way of thinking about the issues, and respect for persons is perhaps more concerned with the holistic approach or the integrity of that person. As a pediatric ethicist, I certainly come down with respect for persons as a much more helpful concept than a pure autonomy based approach.

DR. BERGFELD: Thank you.

Any other comments?

(No response.)

DR. BERGFELD: The question again is to look at the five different designs that the FDA has proposed and discuss one that you might support. Dr. Malone and then Dr. Miller.

DR. MALONE: I'm still wondering what kind of a burden restricting distribution to pharmacies gives patients.

DR. BERGFELD: Can anyone address that? The burden restriction of the pharmacy and how it might restrict a patient's availability to the drug. I gather that's what you meant.

DR. VEGA: The restriction to the pharmacies will include that the pharmacy is required to have some kind of documentation of their compliance in following the instructions when they're dealing with patients. So, they need to produce maybe some documentation that they are complying with the verification process before they dispense the drug.

Does that answer your question? So, there's no burden on patients. This is on the pharmacy.

DR. MALONE: Well, some patients live where there are only one or two pharmacies around and if neither one of those are enrolled in this program, it does become a burden on the patient. So, I'm wondering how many pharmacies enroll in these kind of these things and how

hard it is to enroll.

DR. VEGA: That's an absolute correct concern, and that's why we mentioned among the burdens and the limitations of this specific design that it could reduce or limit the access of Accutane to the patients.

DR. BERGFELD: Dr. Miller, then Dr. King.

DR. MILLER: We had this discussion the other day about the autonomy. This was within the department with the woman who said she would be abstinent and what were we going to do about the contraception. To put it in perspective for you, we're a department of 15. We have 8 faculty and we have 7 people in training. We have celebrated the successes of Accutane over the years. We've used a lot of it. We've adhered to guidelines and we've not had any known catastrophes to date.

So, it is a very serious matter. My concern is those 10 or 15 percent who don't take part in the program, who don't read the literature, the literature that we've been given. There's a lot of it. And people just don't read it. If you're in a department in the middle of the day and your Accutane patient comes in, after the first visit, the question is, gee, what should I order today in addition to the pregnancy test?

I think one of the things that would be truly helpful would be a form from the company which the

physician would fill out as a checklist, or whatever, with each visit indicating not only the pregnancy tests and the contraception, but also the necessary laboratory tests. In that relationship between the physician and the patient, if a decision is made not to use contraception, the physician could so note it in that part of the permanent record. Those forms would be filled out with each visit, which would certainly I think give the company data.

The mandatory enrollment I think is essential, and I don't think that has to really invade the patient's privacy. I think that that can be done again between the physician and the patient and let the physician do the monitoring if there's a problem with the company's doing it.

How does the pharmacist know that this patient is complying, other than a written note from the physician? If the company had an official document or an official form that we filled out and then maybe a tear-off on the bottom and the physician would date that and say, all the guidelines are adhered to, it's okay to dispense the Accutane and I'm giving you the prescription for 30 more Accutane, or whatever the number is, that way the pharmacist would not get into, again, the invasion of the patient's privacy at the counter or whatever.

But I think this would make our lives much

easier. Again, in the department, because there are so many of us, people say, what lab tests or what should I do today? What we did was we brain-stormed and we came up with a list of things that we do. It's printed so that everybody has it in front of him or herself, and this is what I'm going to do on this visit for this Accutane patient. But it would be good to have an official form for each visit that we could keep in a file and that could be used for subsequent data by the company.

DR. BERGFELD: Dr. Miller, in that discussion I was wondering which design that you actually were supporting then, if I could focus you.

DR. MILLER: I was supporting 5 with some modification because I'm concerned about the role that the pharmacist would play in questioning the patient. I don't think that's necessary at all, but I do think the pharmacist needs to be informed, as do nurses and other people, about Accutane. But I think what happens is mainly between the physician and the patient. So, it is 5 with that modification.

DR. BERGFELD: Thank you.

Dr. King?

DR. KING: Well, I was trying to get us to answering the question. Everybody is talking around it. So, I would like to be a centrist and say I would pick

design number 3 because it adds the element of registration and getting a numerator and denominator.

Also the pregnancy test I think would be quite helpful.

I think part of the goal of monitoring is that if at the end of a defined period, the design number 3 is not helpful, then you can move to 4 or 5 because it would be like escalation. If we've taken 18 years to get to this point, I think we could set a goal of a certain defined period to get a numerator and denominator and move from there because the next issue is more onerous and hard to implement. Then the step after that is not at all for females. So, I'd like to go for the centrist number 3.

DR. BERGFELD: Thank you.

Dr. Epps?

DR. EPPS: Yes. In looking at some of the options, we certainly don't want to be burdensome to the pharmacies as well. We've been using thalidomide as sort of a model, but I assure you that the number of female patients on Accutane far outnumbers the number of women on thalidomide. Just the burden to the pharmacies, not only the pharmacists, but are we interacting with a pharmacist or a pharmaceutical aid or a tech? There are a lot of changes going on in the pharmaceutical industry as well that may affect design 5 and implementation. It doesn't

mean it's not worthwhile but it may be difficult to do.

Some of the other designs. Roche's proposal, of course, is more minimal and least burdensome. However, complete participation would also be helpful.

DR. BERGFELD: Dr. Rosenberg.

DR. ROSENBERG: I'm just persuaded by the reasonableness of what everybody has said, even though there are two or three different numbers. They all sound reasonable. But I have a question and I'd like to ask the experts from birth defects and obstetrics and gynecology. All of the ones from 3 on, which seem to have the floor now, include pregnancy testing.

Never mind the details of getting it done and how it's done, whether it's done at home or whatever. And never mind that office visits seem to run on a monthly basis for some reason. If you had your choice of the frequency of pregnancy testing, I'd like to ask what you would think it might be and be useful?

DR. BERGFELD: Dr. Greene, do you want to respond?

DR. GREENE: Well, since the company does distribute pregnancy tests now, can I ask what the sensitivity is of your pregnancy test, approximately what serum HCG level would be detected by your urine test? Do you know?

MS. LEACH: I have a backup slide on that.

DR. GREENE: While they're cuing up that slide, as Dr. Lammer said, the risk of exposure prior to 15 days after fertilization is minimal. The human embryo implants approximately day 7 after fertilization, and a sensitive blood pregnancy test would generally become positive within 7 days of implantation. So, I don't know how that compares to your urine test.

MS. LEACH: I don't think we're going to get the slide that I would like.

The company in its package insert has stated that this pregnancy test is sensitive enough to give you levels of HCG at 4 days. However, the sensitivity of this is guaranteed at 99.9 at 11 days.

DR. GREENE: And that would be 11 days after fertilization?

MS. LEACH: Yes, 11 days after fertilization.

DR. GREENE: So that would be roughly 4 days after implantation.

MS. LEACH: That's right.

DR. BERGFELD: Any other questions? Dr. Cragan?

DR. CRAGAN: That would still be within the period prior to expected embryonic effects. Right?

DR. BERGFELD: Dr. Lammer?

DR. LAMMER: Yes. Despite the fact that the drug's half-life means that after you stop the last dose, some level falling levels are persisting. People typically use the five half-lives. Our observation is that if you stop within 15 days, we've not found problems among those babies even though undoubtedly there's definitely carryover for a couple of days for people who stop around the 14th day or so.

DR. GREENE: But 15 days, in essence, would still be blastocysts. Neurulation doesn't begin until 19 days.

DR. LAMMER: Yes, I agree.

DR. BERGFELD: Well, for us who are not developmental people, that's a good piece of information.

Yes, Dr. Mills.

DR. MILLS: An answer for some of the people about a good time to test if the women have regular cycles would be if they are late with their expected menses. A day or two after expected menses would be a great time for testing. It just wouldn't deal with the entire problem because not all women have regular cycles.

DR. GREENE: And I would add that the incidence of acne is higher among women who do not have regular cycles.

DR. ROSENBERG: What I was driving at is