DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT

ADVISORY COMMITTEE
IN JOINT SESSION WITH THE

DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

Friday, February 27, 2004

8:00 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

PARTICIPANTS

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Kimberly Topper, M.S., Executive Secretary

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Jurgen Venitz, M.D., Ph.D.

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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. GROSS: We would like to begin by reading the Conflict of Interest Statement

Conflict of Interest Statement

MS. TOPPER: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics to be discussed at today's meeting are matters of broad applicability. Unlike issues before a committee in which a particular sponsor's product is discussed, issues of broad applicability involve many sponsors and their products.

All FDA participants have been screened for their financial interests as they may apply to the products and companies that could be affected by the committee's decisions. Based on this review, it has been determined that there is no potential for an actual or apparent conflict of

interest at this meeting with the following exception:

In accordance with 18 U.S.C. 208(b)(3), Dr. Ruth Day has been granted a waiver that permits her to participate fully.

A copy of the waiver statement may be obtained by submitting a written request to the Food and Drug Administration's Office of Management Programs, Division of Freedom of Information HFI-35 at 5600 Fishers Lane in Rockville, Maryland 20857.

Because issues of broad applicability involve many sponsors and their products, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant, and guest speaker.

There will be no industry representative at today's meeting. As you are aware, the Food and Drug Administration has appointed industry representatives who currently serve on each of these committees, but Annette Stemhagen, the industry rep from the Drug Safety and Risk Management Committee, and Peter Kresel, the

industry rep from Dermatologic and Ophthalmic Drugs Advisory Committee, work with sponsors that are directly impacted by the matter before the committee.

FDA has contacted three other industry representatives from other Center for Drug Evaluation and Research Committees that have experience in risk management and with the FDA Advisory Committee process, however, none were available to participate in this meeting.

Dr. Stemhagen and Mr. Kresel are present in the audience and attending as interested observers. Further, we would like to note that Dr. Lou Morris, a member of the Drug Safety and Risk Management Advisory Committee, has been recused from participating in today's meeting. Dr. Morris is also present in the audience and attending as an interested observer.

We would like to remind the FDA participants not to discuss issues at hand outside the advisory committee meeting.

In the event that the discussions involve

any other products or firms not currently on the agenda for which FDA participants have a financial interest, the participants involvement and exclusion will be noted for the record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

Thank you.

Open Public Hearing

DR. GROSS: We will begin with the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationship that you may have with the sponsors of any products in the pharmaceutical category under discussion at today's meeting. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first speaker in the hearing will be Representative Bart Stupak.

MR. STUPAK: Good morning. I do not have any financial interests with anyone, pharmaceuticals or any of the sponsors here today.

Thank you for the opportunity to allow me to address this Accutane Advisory Committee. I

have submitted a written statement, so let me highlight some parts of it.

The FDA has documented 366 pregnancy exposures since the inception of the S.M.A.R.T. program. Because the reporting of the pregnancy exposures to isotretinoin is voluntary, there is no way of knowing how many pregnancies have actually occurred. In fact, Dr. Graham of the FDA has actually estimated the yearly exposure rate may be as high as 2,000, and that has recently been revised, may be as high as 3,500 per year. This, of course, does not include abortions.

It seems clear that the only way to dramatically reduce the rate of pregnancy exposures in Accutane patients is to regulate like the FDA regulates Thalidomide.

A toothless, voluntary registry does not work, and we all know it. The registry should be mandatory for all female and male patients, for all prescribers and dispensers of Accutane. There should be real consequences for refusal to participate in a program. I plan to introduce that

legislation in the coming weeks.

For 22 years, we have seen the harm Accutane can do to pregnant women and to our children. How many more babies have to be born with serious birth defects, how many more women need to have miscarriages, and how many more children have to die before the FDA implements meaningful protections and restrictions on the use of Accutane?

The risk of severe birth defects caused by Accutane is undisputed. Let's take a look at the history of this drug a little bit, because I don't think anyone has ever focused on the full history of this drug.

Go back to the Advisory Committee hearings of 1988, 1989, and 1990. Roche had assured Advisory Committees that Accutane would be prescribed only to women with severe recalcitrant cystic acne and pregnancy exposure rates would dramatically decrease because the average dermatologist would only see less than one female per year that would require Accutane therapy.

Therefore, they concluded it would be limited to 5,000 new patients per year, and Roche's advertising would focus, not on Accutane usage, but future ads would, quote, "dramatically" focus on "contraindication and proper use of pregnancy prevention."

With those assurances, even the 1988 Advisory Committee, by consensus, considered limiting the use, prescription and distribution in four ways, but this consensus was never acted upon and the committee concerns were largely forgotten as Roche went on to make Accutane their second highest selling drug.

Ten years later, the FDA and Roche implemented the Pregnancy Prevention Program after continued pregnancy exposures. In this program, pharmacists, patients, and physicians were to work together to decrease the pregnancy exposures to Accutane.

Despite the PPP, the red stickers, the voluntary consent form, and the NO pregnancy symbol with the red line through it, Accutane pregnancy

exposures continued at unacceptable levels. In fact, many patients, when they saw that pregnancy with the line through it, the women actually thought that Accutane was a form of birth control.

Not only did the number of female patients receiving Accutane dramatically increase, so did the off-label use of Accutane. It is estimated that 90 percent of Accutane use is for off label, and the FDA is of the opinion that many of the prescribing physicians do not understand the teratogenic effects of Accutane.

At the end of the September 2000 Advisory Committee hearing, the Advisory Committee recommended five conditions, and I am sure you are all familiar with them.

The FDA agreed with the Advisory Committee recommendations. FDA and Roche then began their discussions on how to implement these recommendations.

While the focus of these negotiations centered on a pregnancy risk management program, the U.S. House of Representatives became involved

after the death of my son. In October of 2000, my family and I went public with our concerns that Accutane was associated with suicides in some patients. Back then, Roche and the FDA claimed there were 37 suicides. I believe there were at least 54 associated with Accutane use.

Congressional hearings were held in December of 2000 and again on December 11, 2002. The December 2002 congressional Oversight and Investigation Subcommittee hearing was attended by 12 members of the Energy and Commerce Committee.

The answers we sought were to the numerous issues relating to Accutane, but included the continued pregnancy exposure and the psychiatric effects of Accutane. Committee members were appalled when they learned that the FDA had reversed its position and decided it was not necessary to implement the September 2000 Advisory Committee recommendations.

The FDA excuses of privacy and HIPAA concerns for not implementing these recommendations rang hollow with congressional committee members.

In the meantime, Roche continued to aggressively market Accutane, growing to 1.51 million prescriptions in 2001.

The FDA negotiations with Roche produced an agreement called the S.M.A.R.T. program. S.M.A.R.T. did not fulfill the recommendations made by the Advisory Committee. The S.M.A.R.T. program began five months before the December 11, 2002 hearing.

Witnesses from the March of Dimes and the Organization of Teratology Information Services, OTIS, as we call them, testified that the S.M.A.R.T. program would not achieve its objectives, and the S.M.A.R.T. program did not go far enough.

The OTIS representative further testified that a partial review of their organization had already revealed 17 cases of pregnancy exposure to Accutane and that there was a lot of slippage in the system.

At the hearing, the Chairman of our committee asked the FDA, "What is your fallback

position if the S.M.A.R.T. program doesn't improve things with the pregnancy exposures?"

Dr. Woodcock answered that for a variety of reasons, FDA would evoke its authority under the Food, Drug, and Cosmetic Act only as a last resort.

Members of the committee also learned firsthand the FDA was dragging its feet. The FDA failed to provide relevant documentation until the day of the hearing, when they dropped off a number of boxes filled with information requested by the committee.

The FDA had evidence of the failings of the S.M.A.R.T. program from its inception. Doctors were pre-dating yellow stickers that signify the female patient had received a negative pregnancy test. Medical clinics were pre-dating prescriptions so the patient could fill more than one prescription within the seven-day limit of the negative pregnancy test.

At least one patient was purchasing Accutane with no pregnancy test, no prescriptions, no consent forms. Some health care plans, who

electronically dispense their prescriptions, were not using the yellow negative pregnancy sticker.

Pharmacies were not giving out the Med Guides for Accutane, and that compliance with these toothless regulations were not working. In fact, approximately 50 percent of the doctors were not using the informed consent forms because it's voluntary.

The FDA withheld this information from our committee at the December 11th hearing.

Now, Roche said they will support a mandatory registry and submit a proposal. Please understand my and a number of committee members skepticism after going through the numerous Advisory Committee hearings. I still do not believe the FDA and Roche will ever institute a registry and certification program similar to that of S.T.E.P.S. for Thalidomide.

Equivalent effects call for equivalent restrictions. There must be a mandatory isotretinoin registry for patients, doctors, and pharmacists. Pregnancies will continue to occur if

any element is left out of the registry. There must be consequences for failure to comply with any part of the program.

FDA complains that if we do this, we will send this drug to a black market. Since 1999, myself and other members of Congress have tried to address this issue on the Internet. We have asked for the FDA to comment on our legislation, where can we improve upon it. To date, FDA has not answered.

The manufacturer of Accutane, Hoffmann-La Roche, is just as culpable as the FDA in allowing Internet and mail order of Accutane in the country. Roche hides behind the FDA's inaction to complain of Internet sales. Yet, their product coding allows them to determine the exact location of where products are shipped, to whom, and when.

We can cut down on these illegal sales, it can be done. In fact, our committee has convinced Purdue Pharma to stop shipping oxycotin to Mexico as it is being brought back across the U.S. border. Yet, when we pointed this out, what we have been

able to do in Mexico, and that Mexico does not have the same regulatory scheme for Accutane as we have in this country, Roche has refused to stop the shipment of Accutane to Mexico.

Answers as to why Roche isn't really serious about entering into a mandatory registry for Accutane for patients is very clear. Roche did all it could to defeat the registry for Accutane as recommended by the September 2000 Advisory Panel.

In fact, the recommendations or the defeat of those recommendations was a cause to celebrate because, as Roche says, there is no psychiatric registry.

Not only did Roche view the defeat of the registry as a cause to celebrate, and they protected their $450 million sales in Accutane, Roche does not want any form of registry that would provide insight into the psychiatric effects on patients.

Roche is so fearful that a registry may provide evidence of Accutane causing psychiatric injury to young, developing brains that it will

stop at nothing to prevent the registry.

If you go back and take a look at the history of this drug, Roche, in its initial application to the FDA, they forgot to submit a study, a study which was uncovered, which shows that Accutane does adversely affect the central nervous system in mice.

The committee has uncovered three more studies, subsequent studies, that also suggest Accutane does have some effect on the central nervous system. Even the FDA, which has been working with the National Institute of Mental Health and the National Institute of Health has kept from the Advisory Committee and the American people their preliminary studies which do suggest a causation between Accutane and psychiatric injuries. Both the FDA and Roche have misled and failed to protect the American people, unborn children, and young adults from the devastating effect of this drug.

I hope this time the FDA does not allow the manufacturers of Accutane and its generics to

come in and water down the recommendations that may be made by this Advisory Committee.

I am not sure Congress is willing to let them do that anymore. As I said earlier, I will be introducing legislation to establish a mandatory registry of patients, doctors, and pharmacists, similar to that of the Thalidomide registry.

Within the documents provided by the FDA, there is a statement provided by an exasperated FDA investigator who cries out, how could the FDA grant a patent extension on Accutane for use in young patients with the devastation this drug has caused? One begins to ask, what special powers or charm does Roche have over the FDA?

It is time to put restrictions on the users, prescribers, dispensers and marketers of Accutane and its generics.

Thank you and if there is any questions, I will be pleased to answer them.

DR. GROSS: Thank you very much, Representative Stupak.

The second speaker is Gordon Day, who is

President-Elect of the Society of Dermatology Physician Assistants.

MR. DAY: Good morning, Advisory Members.

My name is Gordon Day, and I am a certified physician assistant, and I practice dermatology in Sandy, Utah, a suburb of Salt Lake City.

I am the President-Elect of the Society of Dermatology Physician Assistants. The SDPA is a national medical association of 900 members whose mission is to improve patient care by providing additional education and training for our members.

Physician assistants are but one group of physician providers that prescribe isotretinoin. We are an integral component of the medical team. The collegial and dependent relationship we have with dermatologists contributes directly to the quality of diagnostic and therapeutic care furnished to our patients.

The uniqueness of our position allows us to spend more time with patients, providing education on the therapeutic options for acne

treatment including the risks and benefits of isotretinoin therapy. This also includes contraceptive counseling.

Our Society firmly believes it is necessary to assure the public that our members who prescribe medications such as isotretinoin are qualified to do so. Continuing medical education and other life-long learning opportunities offered by our Society include compliance with the manufacturer-developed and FDA-approved risk management program for fetal exposure.

It is also essential that medical providers using isotretinoin be proactive in ways that guarantee the continued availability of this drug for qualified patients, and that is why I am here today.

There are few other therapeutic options available to us to effectively treat nodulocystic acne. Additionally, it is important to the dermatology health care team that patients be compliant in all aspects of isotretinoin therapy, including adherence to contraceptive practices

which are in place to minimize the likelihood of adverse outcomes.

The importance of isotretinoin cannot be emphasized strongly enough for our patients with severe acne, who can avoid scarring and disfigurement by use of this medication.

As a physician assistant in dermatology, I see older patients on a daily basis who would have benefited from isotretinoin, but whose bouts of this severe acne occurred before this wonder drug was approved for sale in the United States. They will be scarred forever.

I have observed firsthand how patients with severe cystic acne may be so concerned with their appearance that it affects their daily living, self-concept and quality of life. There are patients I care for who will not go swimming because of the severe cystic acne lesions and scarring on their backs and shoulders.

I have female patients that have limited outings socially because of their severe cystic acne, and I have those patients who suffer from low

self-esteem and required psychiatric treatment because of their severe acne. Isotretinoin is an important tool for helping these patients when all other options fail to improve their condition.

In the dermatology practice where I provide care, in an attempt to avoid adverse outcomes, I not only employ the S.M.A.R.T. program, but also have developed a protocol that I and my supervising physician, and other members of our health care team use to make sure that all the necessary risk management program components are documented when using isotretinoin.

This enhanced protocol encompasses review of side effect profiles, pregnancy testing, contraceptive counseling, the completion of time-specific laboratory testing, a thorough review of the patient's own responsibilities, participation in the survey, and completion of the informed consent process.

It is an unfortunate fact that a small number of fetal exposures still occur in female isotretinoin patients, relative to the overall

number of female patients taking this drug.

Therefore, the Society of Dermatology Physician Assistants would like to collaborate with the American Academy of Dermatology Association and the FDA on improving the effectiveness of the current risk management program in ways that lead to fewer adverse outcomes and safeguard patient confidentiality and rights in the health care system.

This process, once completed, should serve as an educational tool for the patients, the prescribers, and the pharmacists.

Thank you.

DR. GROSS: Thank you, Mr. Day.

The third speaker is LaDonna Williams, Executive Director, Inflammatory Skin Disease Institute.

MS. WILLIAMS: Good morning. I am LaDonna Williams, and I am the Executive Director of the Inflammatory Skin Disease Institute, a patient advocacy group that provides education, public awareness, and support to those patients with

inflammatory skin disease and their families.

Inflammatory skin disease is a broad category of conditions ranging in severity. As you can imagine, these diseases are very distressing to those who have them, causing great discomfort and real emotional distress.

You can learn more about inflammatory skin disease by visiting our web site www.isdi.online.org.

I feel it is important to be here today on behalf of the patients who suffer from the inflammatory skin disease acne. Severe acne is characterized by papules, pustules and inflamed nodules. Acne is a common skin disease and can be a very serious medical condition.

For many Americans it is more than a temporary cosmetic problem that can be treated by over-the-counter lotions and creams.

For many Americans it is more than a condition that can be treated by antibiotics, oral contraceptives, or steroids. Indeed, for thousands of unfortunate Americans, acne can be a

life-altering and a socially terminal medical condition for which isotretinoin is the only effective method of treatment.

I am representing hundreds of acne patients who cannot be here today. These patients are both male and female, teenagers and adults who have contacted me to express their strong support for continued access to isotretinoin. This drug literally worked wonders for them and they want to make certain that it remains available for other severe acne sufferers.

You have already reviewed reams of briefing material and listened to hours of testimony about the current risk management effort to reduce fetal exposure to isotretinoin.

The Inflammatory Skin Disease Institute agrees it is necessary to provide and improve a program and reduce the number of pregnancies associated with this drug keeping in mind I have received numerous letters from teenagers and adults stating how isotretinoin saved their skin and their self-esteem.

Many parents have written to me on behalf of their children. One grateful mother told me how isotretinoin improved her daughter's skin, and not only made positive changes in her teenager's life, but made positive changes in the whole family because they could go out in public and do social things together again.

I have received calls in my office from patients and their parents explaining how academics in high school has improved dramatically because attendance became 100 percent after isotretinoin cleared up their student's acne.

One patient had to consider to leave her job that she loved very much because her acne was so severe that her face was in a constant state of being red, swollen, and painful, with disfiguring pustules. Children were afraid of her, which in turn made her withdrawn and depressed. She took isotretinoin and she feels it saved her job, her relationships, and her life.

I could go on and on with personal accounts from patients for whom isotretinoin made a

positive difference in their lives. It is on their behalf that I speak with you today.

I thank you for your time and your attention in listening to these stories, and I hope you will keep these testimonies in mind as you debate the future direction of the isotretinoin risk management program.

If I may close with somewhat of a cliche - the effectiveness of isotretinoin goes beyond skin deep. I hope that I have impressed upon this committee how absolutely essential it is for this drug treatment for acne to remain on the market, and I hope I have impressed upon you how essential it is for the qualified patients

Thank you.

DR. GROSS: Thank you.

The next speaker is Dr. Boni Elewski, President of the American Academy of Dermatology, the fourth speaker.

DR. ELEWSKI: Good morning, everyone.

My name is Dr. Boni Elewski. I am a practicing dermatologist and Professor of

Dermatology in the Department of Dermatology at the University of Alabama in Birmingham.

In addition to my medical duties, I am also President of the American Academy of Dermatology Association. On behalf of the 14,000 members of the Association, and our hundreds of thousands of acne patients, I thank you for the chance to speak with you about the current pregnancy risk management program for isotretinoin.

The health, safety, and welfare of our patients is of paramount importance to dermatologists, as is the integrity of the doctor-patient relationship. Indeed, because of these concerns, our organization is committed to optimizing the safety of our patients taking this drug, as well as ensuring continued access to isotretinoin for all qualified prescribers.

Education and communication with our members and their patients about isotretinoin compliance is essential to the safe use of this drug.

The current risk management program has

been promoted in numerous education and communication efforts, such as CME activities, Member Alerts, articles on our web site, in our official publication Dermatology World, and will be augmented by new initiatives.

In addition, the Association hosted a scientific consensus conference on the safe and optimal use of isotretinoin to which key decisionmakers in the FDA and the scientific community were invited. The proceedings will be published next month.

Recently, the Association sent a letter to the FDA Commissioner with a list of web sites that sell isotretinoin on line. We hope this information will assist the agency with addressing the problem of illicit sales of this powerful drug.

You have just heard a number of compelling stories about the benefits of isotretinoin therapy. I myself have treated hundreds of patients whose quality of life has improved tremendously because of this drug.

This is because acne is not simply a

cosmetic problem. In 1948, renowned dermatologist Dr. Marion Sulzberger said, and I quote, "There is no single disease which causes more psychic trauma, more maladjustment between parents and children, and general insecurity and feelings of inferiority and greater sums of psychic suffering than does acne." More than a half century later, his observation still rings true.

When all other treatment options fail, isotretinoin is the miracle drug that clears away the redness, painful swelling, and lesions of severe, nodulocystic acne, which may lead to painful and disfiguring scars.

Unfortunately, a small number of women are pregnant or become pregnant while taking this drug. As always, our goal is to ensure both patient safety and continued access to isotretinoin for all qualified patients. For this reason, we would like to offer the following recommendations for improving the current risk management program.

First, the survey of female patients should be mandatory, not voluntary. We propose

that isotretinoin therapy be prescribed for qualified female patients only if they participate in the survey. Data generated by this mandatory survey would be more complete. Of course, it is the ultimate responsibility of the female patient to comply with the birth control requirements of the program and to avoid pregnancy.

Second, a single questionnaire and vendor for the female patient survey should be designated. The present situation with the generic manufacturers using one questionnaire and vendor, and Hoffmann-La Roche using another questionnaire and vendor, is confusing to prescribers and patients alike.

Furthermore, differences in the surveys make it difficult to compare data. A single questionnaire and vendor would minimize this confusion, improve data gathering, and promote patient safety and education, and ultimately improve the health, safety, and welfare of our patients taking this drug.

Third, the survey questionnaire should be

re-evaluated and simplified to obtain the pertinent information to assess the risk management program. Ultimately, this will improve the health, safety, and welfare of our patients taking isotretinoin.

Fourth, the current risk management program must be clarified and simplified to address ongoing issues of concern for doctors and patients alike.

And finally, it is crucial that program materials warn patients to avoid Internet sales, avoid re-use, or sharing of isotretinoin.

Let me close by saying, the preservation of the doctor-patient relationship is crucial, and may I add, an integral component to the risk management system. As we strive to improve the current risk management program for isotretinoin, the American Academy of Dermatology Association's guiding principle has always been, and will continue to be, the health, safety and welfare of our patients.

Thank you.

DR. GROSS: Thank you, Dr. Elewski.

The next speaker, the fifth speaker, is attorney Paul Smith.

MR. SMITH: Good morning. My name is Paul Smith and I am an attorney practicing law in Austin, Texas.

My practice relates exclusively to pharmaceutical litigation and for the past two years I have worked nearly full time on behalf of families and individuals who have experienced devastating and catastrophic side effects from Accutane.

In connection with this privilege, I have personally seen and known dozens of individuals and families whose lives have been horribly altered as a result of this powerful and dangerous drug.

The tragedy of a parent who has lost their child to suicide and the tragedy of these parents and babies who have to live with serious and permanent birth defects is beyond description.

I understand that as my role, I am charged with the responsibility to seek redress for these people in the court system. However, today, I am

stepping out of my role as a legal advocate, today, I come before you as a member of the public who has talked to and seen many who have been harmed by Accutane.

Today, I am asking you to take a serious and deliberate look at risk presented by this drug, which has not, in my opinion, been fairly and accurately examined.

You are fortunate to have the ability to suggest and ensure that the tragedies that I have seen in connection with this drug are substantially reduced.

For over 20 years now, the FDA has made an effort to regulate this product by adding warnings and warnings in connection with this drug. This is a laudable goal to try to ensure some safe use of this product, however, as has been well established and is beyond dispute today, the various programs that have been instituted have failed miserably.

The admission and concession by Roche that a registry is needed is too late for many. If there is a registry, however, there are two

components which must be incorporated.

The first involves paternal exposure, that is, where the father takes Accutane when the mother conceives the fetus. This is limited to treatment of the father with Accutane.

The second is the incredible failure of Roche to consider the known psychiatric component of the drug to impair complete compliance with any rational program aimed at preventing fetal exposures.

The dangers and risk of paternal exposure is something that must be better studied and understood. I point you to the Thalidomide warnings which strongly advised male patients taking Thalidomide to use contraceptive measures. This is in dramatic contrast to the Accutane, which suggests that there is no risk to the fetus as the result of paternal exposure.

I have with me recently released documents that indicates that Roche's own internal experts has, in reviewing 13 potential paternal exposures, found that in 5 of those cases, a possible

relationship could not be excluded.

This is a document that Roche fought hard to keep from the public. I have it here with me. It is sitting here for your review. I would welcome and request that you get a copy of this and review it thoroughly.

Carter Crosland, who is here with his mother and father, is, in fact, one of the five whose medical records were examined by the Roche's internal geneticist. The Roche consultant concluded that Carter's difficulties could very well be related to Accutane embryopathy.

Roche's response to this phenomena and the risk associated with paternal exposure is inadequate. The public should be aware the potential exposure does exist, and there should be warnings specifically advising that there is problem with paternal exposure.

We would strongly urge a registry that includes males using Accutane that specifically tracks their sexual activities.

The second issue for your consideration is

the inability of certain patients to comply with warning and instructions as a direct result of known psychiatric side effects presented by this drug.

Only Roche disputes that Accutane may cause depression and behavioral changes. It seems to be well accepted within the rest of the scientific community that there is a strong relationship between Accutane and psychiatric adverse events and depression.

I have seen nothing publicly which suggests that Roche has even considered this foreseeable and predictable phenomenon of pregnancy secondary to impaired capacity as a result of depression.

Debbie Banner is here to explain to you how she got depressed and was unable to comply with the program in effect at the time to prevent her pregnancy.

I thank you for your attention and your kind consideration and again the paternal exposure study itself that was submitted to the FDA is here

for your review.

Thank you very much.

DR. GROSS: Thank you, Mr. Smith.

The sixth speaker is Debbie Banner.

MS. BANNER: Good morning. My name is Debbie Banner. I am here with my husband Kevin. I have known my husband since I was 17, and we have been married for seven years. I appreciate this opportunity to share with the members of this honorable committee my horrifying experience with the drug Accutane.

Starting today, we will offer one of the answers to this question, why are girls continuing to become pregnant while on Accutane despite the warnings that Accutane causes birth defects?

I am afraid that one of the answers I will propose today is one that neither the FDA, this committee, or Hoffmann-La Roche has adequately studied or considered.

I am also here to describe the nightmare of having a child who has been born with Accutane birth defects.

I became pregnant while on Accutane. I survived this nightmare by the grace of God, strong faith, a loving husband, and an overwhelming commitment to my son.

I was devastated that I played a role in causing my own child to be deformed. So, I vowed to sacrifice everything to give him the best life I could possibly give. Because I accepted my fate humbly, I believe that is why God finally revealed the other side of the story to me, the missing piece of the puzzle.

On October 4th, 1996, my son Deven was born. There is no medical doubt that his birth defects are due to the effect of Accutane on him as a developing fetus. He has been seen by the best physicians and was diagnosed with Accutane embryopathy.

Deven was diagnosed with an underdeveloped cerebellum resulting in cerebral palsy and hypotonia. At the age of 7, he is fed through a feeding tube that is surgically inserted into his stomach, he suffers from seizures.

After four eye surgeries, he has visual perceptual problems. He has sensory integration problems which manifest as autistic-like behaviors. He has verbal expressive disorder, speech problems, and requires physical therapy, occupational therapy, and speech therapy.

He has a chronic history of pneumonia. He requires special education services in school and special accommodations. Along with these and other medical problems, as well as fine motor and gross motor impairments, it is likely that he will be unable to take care of himself as an adult.

I was on Accutane in 1995 when I was 24 years old. I was an aerobics instructor and attending school. I was working two jobs. I was of healthy mind, body, and spirit, so when I first visited the dermatologist, I was a happy person although I had an acne problem.

Days after ingesting Accutane, I began to react as if I were poisoned. I developed severe headaches and sharp, piercing head pains. I was nauseous day and night. I was weak, dizzy,

confused, forgetful, suffering from hypersomnia and severe crying spells.

Eventually, I developed suicidal thoughts. I just wanted to sleep and never wake up again. I was too sick when I was awake.

At the initiation of treatment, I had chosen abstinence as my method of birth control. I chose this for religious reasons and did not plan to be sexually active again until I was married.

However, once in a state of severe depression, I became mentally incapable of making appropriate decisions. My thoughts were filled with thoughts of suicide and death, which eventually required psychiatric intervention.

At the time of conception, I was no longer a patient that was reliable and capable of complying with mandatory pregnancy prevention procedures and reliable in carrying out instructions.

The missing piece of the puzzle was given to me when I learned that the psychiatric problems that led to my pregnancy were a side effect of

Accutane.

Through my research, I have now met other mothers who became pregnant on Accutane. I have learned that depression was a factor in their inability to comply with the warnings that, like me, led to a nightmare of birth defects.

I have spoken to one mother who actually attempted suicide while on Accutane and became pregnant weeks later. To this day, there is no instruction, education, or warning on how psychiatric side effects of this drug may prevent you, despite the best intentions, from complying with the pregnancy prevention program.

It seems fundamental to me now, but how can you educate someone that may not be able to protect themselves. How can anyone including the doctors who prescribe it believe that the drug could do this when Roche refuses to admit that there is a psychiatric component to the drug?

I am here to tell you from my own experience, and experience told to me by other mothers admitted in a cloud of shame and stigma

that depression can and does interfere with pregnancy prevention even when patients have chosen other forms of birth control.

Because women and girls are continuing to become pregnant, I plead with this committee to require that females of childbearing potential receive an initial psychiatric evaluation and are then monitored by a psychiatrist throughout treatment.

To leave this decision to patients who may be in denial and cannot protect themselves is to guarantee more birth defects and abortions. Because Accutane is such a powerful drug, it is worth the extra effort and expense to save children from a lifetime of deformity and pain and to finally bring an end to the outrageous number of Accutane abortions.

Warning is simply not enough when psychiatric side effects are involved.

In conclusion, I want to express my sympathy for people suffering from acne, but even in the very worst cases of acne, their suffering

cannot compare to the suffering endured daily by children born with Accutane birth defects.

Thank you.

DR. GROSS: Thank you, Debbie, and Kevin Banner.

The seventh speaker is Carter Crosland.

MR. CROSLAND: Good morning. My name is Carter Crosland.

Today, you will hear my story. Not only do I speak for myself, but also for the hundreds, perhaps thousands of children whose voices will never be heard. Those dreams and hopes will never be realized. Today, I am their voice.

I was born January 22, 1985, in a small rural town in central Utah, the first child of my parents. As a young boy, I was told that I was a miracle and that I had something important to share with the world. I have been blessed with the health, strength, and mental faculties to speak before you today. Perhaps that is my purpose.

As a young boy, I dreamed of being a wrestler. I loved sports and had an unusual talent

for learning statistics. I played T ball with my friends and they ran the bases for me while I stopped the ball with my wheelchair tires.

And then the boys moved on to minors and majors and I stayed behind. I became the batboy and then the base ump. Then the coach, manager, or anything else just to stay involved. The same was true with football and wrestling. As I matured, I realized I would be left behind again. Not only in sports, but in every single aspect of my life.

My parents sacrificed to get me where I am, and because they worked hard, we didn't qualify for disability funding from the government. I was too smart. I passed all the cognitive tests, despite missing a third of my brain to a cyst.

I passed all the skills and vocabulary tests. I could even pick up the blocks with my mouth and put them in the holes quickly. Therefore, by their standards, I wasn't disabled, and I was at the end of the waiting list without assistance.

I had generous people who helped me get

arms as a young boy, but we couldn't keep up with the constant re-fitting and trips to the city. My mom worked full time to keep insurance for me, but she couldn't keep leaving work for sick kids and trips to the prosthetic specialist, so I gave up on the arms. They were too costly.

When I entered first grade, my mom quit work, so that I could go on field trips, birthday parties, and to the library with my friends. Where I went, my chair went, and also my parents and my van went. That made our financial situation even worse, but I appreciated having my mom around.

I took drivers ed at 15 and passed with flying colors, well, all except for the driving test. You see, I can't afford the car for me to drive and the school district can't provide it. I completed high school and graduated with my class. I was voted most preferred senior probably because I had the gift of gab and I like to visit with everyone.

My school built a ramp so that I could participate in pomp and circumstance with my peers.

I now attend college and I am studying communications. I hope to be a sports broadcaster or work for some firm as a public relations guy.

My voice is the only asset I have that puts me on the same playing field as those around me. It is literally the only thing I can do on my own. This is what I have accomplished so far in my life against all odds. Now I would like to tell you what I cannot do.

I room with a friend at college. I pay him to help me bathe, get dressed, cook my meals, charge my wheelchair, get my books, help me on dates, drive my car, and anything else I want to do. My friends lift me up the stairs to their place or to any other place that is not accessible.

I have to plan for bathroom breaks because I need help. My friend will get married soon, and I will find another person and then another, and another. My parents travel to bring me home and back on weekends because I cannot afford a car that I can drive on my own. My buddies take me shopping and help prepare and eat my meals. They clean up

for me and do my wash.

Because I have all my mental faculties, my dreams are the same as every other young man my age - a car, a job, a girlfriend, and someday a wife and family. I hope for these things, but I take it one day at a time, and I don't know what the future holds for me.

I keep being determined to make the best of it and to find happiness in every small thing around me. Some of these dreams I can realize now if I could afford it. Money is a tremendous limitation, nearly as limiting as my disability. Please do not make money a factor in your decision to research and regulate this drug.

They say that I don't fit into any category or syndrome because of my intelligence. I feel that my mental abilities are a gift from God and are for a purpose. Today, I hope that purpose is to bring this matter before you to your attention.

I hope that you will look deep into your heart and do everything you can to study, research,

and take every step possible to prevent this from happening to one more child. Most are not as fortunate as I am. Their voices will never be heard. Please hear mine.

I thank you for your time.

DR. GROSS: Thank you, Mr. Crosland.

The eighth speaker will be Lisa Crosland.

MRS. CROSLAND: Ladies and gentlemen, good morning. I am Lisa Crosland, and I am here with my husband Russell and my son.

A first pregnancy is supposed to be a happy time filled with anticipation and excitement, but mine was neither. For me, I was a 19-year-old in college, in love. We had big plans, big plans and dreams that included marriage and children, but things changed when Russell began using Accutane.

Our relationship became a disaster filled with unkept promises and unpredictable behavior. An engagement was broken and so was my heart, and then I found out I was pregnant and alone.

Things went from bad to worse. I had recurring nightmares that the baby inside me was

not right. I didn't grow enough, the baby banged back and forth. An ultrasound at almost six months confirmed my worst nightmare.

We were told that our baby had no arms and legs, no sex organs. The child had a third of its brain covered with fluid that was increasing. They felt his eyes were too big and his head too large. A large growing hernia and funny-shaped mouth was also evident.

Most doctors felt the child would abort itself. Others said that if it lived, it would be on life support, unable to suck, and institutionalized. I was devastated and so was Russell. We prayed for a miracle that our child would not suffer.

Our miracle was not what we expected, our child lived, and today we are telling his story. As parents, our first concern was why did this happen, what did I do. Parents need to know why this has happened to them.

I had lived what I thought was a clean and healthy life. I did not smoke, I did not drink or

use drugs. Every effort was made to determine what I could have done to prevent this as a mother. Yet, we turned up empty-handed.

The first time I heard the word Accutane embryopathy was from a genetics counselor at the University Hospital in Salt Lake City. Carter was almost three months old and had just had his second surgery. The doctor felt Carter's symptoms were too similar to maternal Accutane exposure to ignore.

I told her that I had never used the drug, but his father had before, during, and after I became pregnant. Carter has been worked up by the best doctors and the best facilities. Everyone wanted to know whether Russell or I carried some odd genetic code that would cause this in the future.

We looked everywhere, but there was nothing else but Accutane. We reported an adverse reaction to Hoffmann-La Roche, who responded that this could not be the cause of our child's deformities. A few years later I spoke directly to

a doctor at Hoffmann-La Roche who told me that there were a few other reports of paternal exposure, but all could be attributed to another cause.

I even asked for and received films and study materials from Roche. You see, as we have now learned from Roche's internal documents made public only after Roche fought and lost the battle to keep it private. Carter has all the clinical signs of Accutane embryopathy.

Roche initially agreed that paternal exposure to Accutane could not be ruled out. Why then hasn't this been researched? Are kids like Carter not worth it?

Since this time, I have seen warning labels and adverse reports increase, more children aborted and affected. I have studied and found more and more similarities to things Carter was experiencing in his life that other children whose mothers were exposed were experiencing.

His mouth, his dental problems, his problems with temperature regulation are just a few

of the less visible problems. Some children whose only link is a mental I.Q. of under 85 have been attributed to Accutane. I find it impossible not to include Carter in this category simply because his father was the user and he is normal in intelligence.

Of course, it may very well be that women who become pregnant from a father who has taken Accutane may never put the issue together. The possibilities of hundreds and thousands of abortions simply attributed to poor development or unwanted pregnancy may have occurred, with the public being kept in the dark of these risks.

The fact that there has not been more reporting of this issue does not mean that there is not a serious risk and danger. It only means that Roche has been successful in keeping this from the public.

This drug Accutane has devastated my family emotionally, physically, and financially. It has been carelessly over-prescribed and under-regulated. It has destroyed our dreams and

shattered our lives, yet we stand before you today united in our efforts to demand a change.

We want adequate research and funding into the possibility of paternal exposure of retinoids. We want the prescription of this drug for dermatological reasons restricted to dermatologists who are forced to prescribe it only as a last resort for both men and women.

We want those greedy individuals who facilitate unprescribed Internet sales of this drug stopped and prosecuted.

Most of all, we want answers, not only for ourselves, but for the hundreds of babies aborted who may very well be exactly like Carter, but discarded.

I cannot stand before you today and tell you exactly how Accutane is responsible for my son's disabilities, only that we know that it is. Our family and many others have suffered long enough at the hands of Hoffmann-La Roche. We urge you to take a stand and ensure the safety of this drug.

Thank you for your time.

DR. GROSS: Thank you, Mrs. Crosland.

Is there anyone from the public who wants to speak at this point?

[No response.]

DR. GROSS: Hearing none, we will declare a recess at this point, and we will reconvene at 9:15.

[Break.]

DR. GROSS: While we had closed our public hearing, we are going to reopen it briefly. The tenth speaker from earlier today, Jeffrey Federman will speak.

MR. FEDERMAN: Good morning. My name is Jeff Federman, and I am President of Paragon Rex, a company that provides services to the pharmaceutical industry.

For purposes of disclosure, we are not engaged with the manufacturers involved in today's meeting. In addition, my colleagues and I authored a book about pharmaceutical risk management.

Let me begin my proposing that today's

proceedings provide two insights about what can reasonably be expected about the design and improvement of risk management programs.

The first focus is on the expectations of rigor and precision. We are all associated with a pharmaceutical industry that is famous for the rigor and precision of its well-controlled clinical trials. We expect to be able to determine drug efficacy using scientific and statistical methods, and would hope to bring a similar level of rigor to pharmaceutical risk management.

Our colleagues in other risk-intensive industries, such as nuclear energy and aerospace, have much to teach us about applying a similar degree of rigor to risk assessment and program design. Validated well-established methodologies exist to guide the design of risk management programs in these industries.

Research of these practices, as well as the disease management and adult learning disciplines, suggest that effective drug risk management may have several key elements.

1. Evidence-based assessment and design process, perhaps such as failure mode and effects analysis, or FMEA, that targets interventions to address specific process-related causes of failure.

2. Redundancies that back up the inevitable human failures.

3. Collaborative design with practicing physicians to help program elements fit seamlessly into their day-to-day practice of medicine.

4. Predictive modeling or pre-testing to determine the likely effectiveness of any proposed program and anticipate where program weaknesses may exist.

5. Innovative implementation approaches, perhaps such as scenario-based learning, that build on the way clinicians and patients learn.

Finally, ongoing monitoring and measurement with the anticipation that initial programs change over time.

Certainly, rigorous design is achievable, yet, in the world of every-day clinical practice, where care is delivered based on the judgments and

knowledge and motivations of well-meaning men and women, high precision in terms of predicting program compliance and use may be an unrealistic expectation at the time of program introduction.

This key difference between the controlled clinical trial environment to which we are accustomed and the realities of clinical practice lead to a second expectation.

I suggest that expecting a definitive precise or final design at the time of risk management program introduction may not be reasonable. Quality improvement standards in other industries are built on the foundation of continuous quality improvement, or CQI.

The concept of intervening with an initial program, then, monitoring and measuring for early opportunities to improve the program may be a more achievable expectation.

The approach of showing continuous movement towards a goal may require a frequency of analysis and potential redesign occurring in intervals of months, not years.

Today's discussions are another step in the ongoing improvement of Roche's pioneering PPP and enhanced S.M.A.R.T. programs. We support these FDA initiatives and believe these hearings today will help lead to the next generation of effective pharmaceutical risk management programs that incorporate both rigorous evidence-based program design, as well as continuous quality improvement to provide the degree of product we are all seeking to achieve.

Thank you.

DR. GROSS: Thank you, Mr. Federman.

At this point, we will close the open public hearing again, and we will move on to some other orders of business.

Allen Mitchell, Director, Slone Epidemiology Center, Boston University, will have a few minutes to comment on some questions that were raised yesterday.

DR. MITCHELL: Thank you very much, Dr. Gross, and committee, I really appreciate your offer of a few minutes to respond to some of the

concerns raised in the FDA review.

Yesterday, I mentioned that I was not here on behalf or speaking for the FDA, and then this morning's remarks, I just want to point out that not only is that the case for these remarks, but I am not speaking on behalf of the generic sponsors or Hoffmann-La Roche. I guess that leaves me speaking on behalf of the Slone Epidemiology Center, which I think they will allow me to do.

This presentation has not been shared with anyone other than our own group.

[Pause.]

DR. GROSS: We have a few questions from yesterday. I would like to start with Dr. Day.

DR. DAY: Thank you. I did have questions yesterday, however, I would like to defer that comment and use it for an additional comment on the questions today.

Would that be all right, Dr. Gross?

DR. GROSS: That's fine.

Dr. Bigby.

DR. BIGBY: I have a couple of questions.

The first is to Hoffmann-La Roche.

The question was asked I think yesterday about annual sales, and you found the number, but didn't say what it was, the number of 450 million came out today.

What are the annual sales of Accutane?

MS. REILLY: What year, sir?

DR. BIGBY: Last year.

MS. REILLY: In 2003, our U.S. net sales were $144 million.

DR. BIGBY: Do you have any idea sort of what you have spent in terms of legal fees and lawsuits around the issue of teratogenicity?

MS. REILLY: No, sir, I do not.

DR. BIGBY: Is that an obtainable figure?

MS. REILLY: I would defer to our counsel.

DR. GROSS: Dr. Cohen, Michael, did you have a question from yesterday?

DR. COHEN: No, I will hold it until a discussion later.

DR. GROSS: Dr. Katz.

DR. KATZ: I wanted to ask Dr. Huber, on

the people who enroll, what percentage of those, how soon do they get a notice that they have enrolled do they get a questionnaire, and what percentage of the people that enroll fill out those questionnaires, the two or three questionnaires they get?

On the enrollment form, it says you will get two or three questionnaires through the treatment. So, what percentage of the people that enroll get the questionnaires and answer them, and how quickly do they get them?

DR. HUBER: I will refer to Dr. Blesch who will answer your question.

DR. BLESCH: The Accutane survey is divided into two sections. Eighty percent of the patients who enroll, 80 percent get questionnaires immediately upon enrollment. The other 20 percent get a questionnaire approximately six months after they enroll, and then a final questionnaire six months after they finish treatment.

All Accutane-surveyed patients are followed, continue to receive questionnaires until

six months after their treatment has stopped.

DR. KATZ: What percentage of patients who you send that questionnaire to fill out the questionnaire?

DR. BLESCH: I don't have that exact number, but I believe it is about 80 percent.

DR. KATZ: Thank you.

DR. GROSS: Then, the last question from yesterday was from Mr. Levin.

MR. LEVIN: I will defer questions until later, but I do have one.

I am just curious what the sales for Accutane for Roche were in 2002, prior to generic entry into the market.

MS. REILLY: In 2002, that year to date figure was 380 million.

DR. GROSS: Thank you.

Before proceeding, I would like to read a comment that Dr. Jackie Gardner suggested I read, and I concur.

We would like to publicly thank the people who came forward during the open public hearing

with their personal stories and acknowledge how difficult that was.

Thank you.

Allen Mitchell.

Responses from Slone Epidemiology Center

DR. MITCHELL: Thank you. I think we have things working.

[Slide.]

If I can follow up on Dr. Katz's question from our survey, which is a similar design, the response rate to the during and after treatment questionnaires, the questionnaires that are sent to women at the onset of therapy and the midst of therapy is about 97 percent in our survey. It is extremely high. That is both with mail and telephone responses included.

I wanted to speak about the limitations of the voluntary isotretinoin survey and perhaps some of the non-limitations because it seems to us that this is a critical issue in interpreting the data.

[Slide.]

Quickly, to review some of the questions,

and these are questions that we have posed as potential limitations to this or any other survey since 1988 when we first designed it, what is success. The committee is struggling with this.

Of course, there were no pre- and post-comparisons possible, and here we are talking about the data up until the onset of S.M.A.R.T. These are the 14 years of data preceding S.M.A.R.T.

What are the critical events that one judges success by, is it pregnancies, live born infants, infants with birth defects? Is the critical outcome a rate of pregnancy, or is it an absolute number?

One could imagine different scenarios with very different responses to that final question.

[Slide.]

Two other limitations that we have identified is that survey participation may provide an unintended intervention and also that recall of risk management may be biased among women who become pregnant.

We were well aware of those two concerns

going into it, and to deal with those concerns, the design, which is admittedly complicated, includes two arms, the AT arm, which is the after therapy only interview, if you will, and the DAT arm, which is the during and after therapy interview with a number of contacts with patients throughout the course of therapy.

Those have varying degrees of patient contact, and information in those arms is collected either prospectively or retrospectively with respect to some of these behaviors. So, we think that we have been able to deal with those issues.

[Slide.]

There is another point about whether the reporting of pregnancies among survey participants is credible. We are, of course, concerned about that. If women are avoiding pregnancy during treatment, one would expect a rebound in pregnancy rates following treatment. That seemed to us to be an indirect measure of whether reports may be accurate.

[Slide.]

We have lifted this figure from our 1995 New England Journal paper, which summarized the survey experience to date at that point, to describe the pregnancy rates and outcomes during and after isotretinoin therapy.

I think it becomes fairly clear that during treatment now, which is lumped together, the pregnancy rate is somewhere approximately 9 per 1,000 person years. We are using person years here.

And as you can also see, elective termination represents about 70 percent roughly of those pregnancies. In the one month after treatment, where the risk of malformation is considerably reduced, and in our data doesn't show much increase at all, but in that one month of therapy, you begin to see the pregnancy rates increase, and in the two months, three months, and four months after therapy--and we only go out to four months--what you find is a considerable rebound in the pregnancy rates, which is what one would expect if women are trying to avoid pregnancy

during the course of therapy.

But it is also interesting to point out that by the time you get to the fourth month, the proportion of pregnancies that result in elective termination approximates what we see for the U.S. population.

So, this provides some indirect assurance that reporting is not terribly inaccurate.

[Slide.]

But what I want to focus on is the issue of whether voluntary enrollment may compromise representativeness, and, of course, one always worries about that.

The response to that concern is to maximize enrollment. We all know that, that is basic epidemiology.

[Slide.]

The second approach is to compare the survey population to the target population, and to do that, using demographic characteristics, on the one hand, and ideally, the risk factors in the two groups, on the other hand.

[Slide.]

I think we should make the point and understand clearly that enrolling 60 percent or more of the target population does not, in itself, assure that that population is representative.

Conversely, enrolling less than 60 percent of the target population does not assure that the sample is unrepresentative, and I think that there has been a fair amount of assumption that because the enrollment rates are below 60 percent, therefore, the sample population is unrepresentative.

[Slide.]

It is very difficult to make direct comparisons in trying to respond to the question about is the survey population a biased sample, and we could spend days, as we have, we have spent months over the past 14 years struggling with how to evaluate this, the best we can do, and this is based, not only in our own considerations, but suggestions from FDA and from advisory committees and our own advisory committee that we have, is to

do some indirect comparisons.

These are necessarily limited and imperfect, and I wish to make that very clear.

[Slide.]

Two parts of data that I want to present were alluded to in the FDA review document. One was a comparison we did using United Health Care data, which is a large plan that had I think 14 different prescription plans under one umbrella.

What we were able to do through a complicated process was to compare women who had received a prescription for Accutane through that plan, and look at those who enrolled in our survey and those who didn't enroll.

[Slide.]

There were very few variables that we could identify for comparison, but one of them was age, and what we found was that the age among the Accutane participants was somewhat younger by about two years than it was in the population that didn't enroll in the survey. This was actually compatible with some anecdotal reports which we frankly didn't

believe from one of our colleagues at Roche at the time.

This was back in the beginning of the survey, in the '90s, who had said that in his conversations with providers, he was finding a number of them reporting to him that they tried to have women participate in the survey if they felt that woman was at increased risk, that they felt that the survey would provide some additional intervention or a component that would help encourage compliance. It might do that indirectly, but it certainly isn't the purpose of the survey.

[Slide.]

So, this was compatible in that one would expect that women who are older would be at less risk for pregnancy, and, indeed, when you stratify these findings according to age, and now we are looking at this time the participation rate in the survey was estimated to be about 40 percent, what we found was that that 40 percent rate was fairly consistent across the three youngest age strata. Where the participation rates were lowest were in

the oldest group of women, and, in fact, among the women 50 to 59 years old, only 14 percent participated, which would be compatible with the either subselection or doctor's selection of women at low risk saying don't both participating in the survey, you are not at risk for pregnancy.

[Slide.]

The other data alluded to in the FDA review, and that we have cited, and these are again previously presented data, is a consumer survey that was conducted by Roche identifying a number of women who had been prescribed Accutane, and asking them whether they enrolled in the survey or not, and interestingly enough, the age difference was again about two years, that the enrolled women tended to be about two years younger than those who didn't enroll in the survey.

Median education wasn't terribly different, the source of their prescription wasn't terribly different, indeed, the women in the survey, 10 percent more than the women who weren't in the survey reported being sexually active, and

not surprisingly, along with that, higher rates of contraception use.

Now, one of the things cited in the FDA report was that, well, gee whiz, if you look at this population, use of the birth control pill was reported by 40 percent of the women enrolled in the Slone survey, but only 16 percent among the women who did not enroll.

On the face of it, there is no question there is a difference there. It is not accounted for by condom use or other barrier methods, but it is striking that the surgical sterilization rates were compensatorily different among the enrolled and unenrolled women, and if you add up the highly effective contraceptive methods as a percent, what you find is that they are virtually identical in terms of highly effective contraception use among the women in the survey and the women who chose not to participate in the survey.

[Slide.]

But again, even within this analysis, there is about three times as many women--two and a

half times as many women on the pill in the survey, suggesting that again, if anything, the survey population may be at higher risk for pregnancy since surgical sterilization is a highly effective and more effective method than the pill.

[Slide.]

Finally, bringing us to the most recent data, we compared the survey data, as did FDA, versus isotretinoin users according to age--and this is in the one year before S.M.A.R.T., and we used the FDA data presented for advanced PCS as representing the base population, the target population, and we have provided the survey age distributions on the left.

I think most observers would say that this is actually, until you get to the older age groups for sure, pretty representative, and while there is a decrease in the proportion of participants who are 15 years of age or under, that decrease is relatively small, where again we see a deficit of participation that is fairly consistent is again in the older women who are less at risk for pregnancy

by and large.

[Slide.]

And, indeed, when you compare the pregnancies-- this is again in the year pre-S.M.A.R.T.--reported by our survey, and the total reported by FDA including the spontaneous reports, we see striking similarities in the distributions.

[Slide.]

So, in answer to the question is the survey population a biased sample, to us, the evidence does not suggest that the survey population is biased towards women at low risk of pregnancy.

Indeed, the indirect evidence, and I stress it is indirect, suggests that, if anything, the survey disproportionately includes women at relatively high risk of pregnancy, and this pattern has been observed consistently at various points in the survey's history.

[Slide.]

That brings us back to this figure that we

showed in our presentation yesterday, where we observed, again in the pre-S.M.A.R.T. era, 14 years experience, a decrease in the pregnancy rate from roughly 4-fold to a little bit over 1-fold, a rather striking and consistent decrease over time.

[Slide.]

Well, if the survey has any value, we need to consider what this means, and we think this trend is unlikely to be explained by enrollment biases, which would have to have changed over the 14-year period.

We have done all sorts of models as to how one might account for this trend through biases, and it is very difficult to come up with one.

[Slide.]

Rather, we think it may reflect continuing improvements in the implementation of the risk management program via its incorporation into routine practice and I might add residency training programs and the dermatology programs, so that our summary view is that without respect to S.M.A.R.T. specifically, we do think that the 14 years

experience preceding S.M.A.R.T. does reflect incorporation of risk management elements to the point where they have actually appeared to result in a fairly substantial decrease in the pregnancy rates.

I will be happy to take questions, and thank you for your consideration.

DR. GROSS: Are there any questions? Yes.

DR. KIBBE: My question deals with the characteristics of the individuals in the two groups, those that undergo therapy and don't get pregnant, and those that undergo therapy and end up having either been pregnant when they start or end up getting pregnant during the time frame.

I guess we could say that 99 percent of the women who enroll in therapy are successful in not having a pregnancy occur during that, and 1 or 2 percent do, but what characterizes the differences between those two groups, because if we want to improve what we do, we don't have to change it for the 98 percent who go through the process effectively, but if we could find some handle that

would help our clinicians identify individuals that needed an additional activity or procedure, it would help us a lot.

DR. MITCHELL: Actually, it is obviously a relevant question. First of all, from these data in the most recent years preceding S.M.A.R.T., the pregnancy rate would be 99.9 percent, it's roughly 1 in 1,000. I don't mean to quibble, but it is useful to keep that in mind.

What we would call the analysis you are describing is a risk factor analysis. What one of the public speakers called it was a failure mode and effects analysis.

We are in the midst at the present time frankly in doing a detailed analysis of exactly that consideration. We have certainly identified crudely that there are no gross characteristics that appear to predict an increased risk of pregnancy.

As one might expect, we have seen the chosen method of birth control is directly related to the risk of pregnancy. We have seen that the

typically effective methods are effective and the typically ineffective methods are ineffective.

We have also seen and published in this paper in 1995, our experience which indicates that for any given mode of contraception, we provide data to suggest considerably higher efficacy than the generally published data on efficacy, and that is because we think the motivation of this population is unusually high.

What we are doing now is looking at all the elements in the Pregnancy Prevention Program, the pre-S.M.A.R.T. Pregnancy Prevention Program, to see if we can identify any elements that do exactly what you are describing, that characterize the women who become pregnant and distinguish those women from the women who did not become pregnant, so that interventions could be targeted to that population, and we are hoping to have that completed--Dr. Trussel, James Trussel is going to be joining us in that analysis as he has in the past--and we hope to have completed in the next few months.

DR. KIBBE: A second question has to do with my interest in the international experiences, if you will, with this medication. Roche has said that they have never had a country ask them to take it off the market, but I can't imagine that there aren't countries that are interested in eliminating the risks.

Do you have any access to any data that would help us understand how their interventions differ from ours and how their risk ratios might differ from ours, and how that might impact our decisionmaking?

DR. MITCHELL: The short answer is no, we don't have any data and we have certainly tried to find such data. One of the concerns that we have is that the way drugs are managed philosophically in some other countries, and particularly one scandinavian country with which I am aware, is very different culturally from the U.S.

In one country, the attitude was that we do what we do and after that it is not our concern, and they don't track the outcomes of exposures, not

pregnancy exposures, but even pregnancy rates.

I think the U.S. is frankly, uniquely providing information that has a denominator. Other countries have not, to our knowledge, taken this concern nearly as seriously as it has been taken in the U.S., and the result is that there is very little data.

DR. GROSS: Thank you, Dr. Kibbe, for your questions.

The next question comes from Dr. Honein.

DR. HONEIN: Yes. Dr. Mitchell, you mentioned 38 to 45 percent survey enrollment based on the United Health Care survey for 1990 to 1996. Yesterday, the FDA presented data suggesting a 19 percent survey enrollment for the year prior to S.M.A.R.T.

Was there that much decline in enrollment in the survey over that time period, or is this a different methodology for calculating the estimated survey participation?

DR. MITCHELL: The methodologies by which you calculate participation requires that you know

what the denominator is, and the denominator is the number of unique women taking the drug.

The difficulty in establishing that denominator, the difficulties are considerable, and we have had a lot of debates over the years about what is an appropriate denominator.

I mean if you simply divide the total number of female scripts by 3.7, as the FDA used the figure from one experience in the Seattle area, you come up with one estimate of a denominator. If you divide that by 4 prescriptions or 2 prescriptions, you get very different denominators. The Kaiser data I think were closer to what we use.

But the fact is that we do suspect, based on indirect evidence, that participation rates declined over time, and it was really because of our concern that we focused a lot of attention on does the decline also reflect some differences in the way women are enrolling.

What we think, although we can't prove, is that the $10 incentive, which we identified at the outset of the survey back in '89 as an incentive to

get women to participate in the survey through the medication package which we came up with the idea of putting the enrollment form in the medication package to bypass the physicians who may not want women to participate or may not encourage them.

So, we said, you know, make it like a toaster rebate coupon and encourage women who might be noncompliant to participate. But that was a $10 incentive back in 1989, and one of the reasons for increasing the incentive in the most recent efforts was to adjust, if you will, for inflation that $10 incentive. So, we do think that there has been a decline.

DR. GROSS: The next question is from Dr. Wilkerson.

DR. WILKERSON: Considering best practices once again, considering the women that we have, the ages, the methods of birth control that they have employed and reasonable rates of success of those programs, what would be your calculated rate of pregnancies per 1,000 cases if everybody did exactly what they were supposed to do and they used

the methods which are they using, what would this rate actually look like? Instead of being 1 per 1,000 courses of therapy, how much would it go down to?

DR. MITCHELL: Can I turn your question a little bit?

DR. WILKERSON: It depends.

DR. MITCHELL: I can't give you the answer. Okay, I can't give you the answer, but I want to understand the question, so we could give you the answer.

DR. WILKERSON: In other words, if you take the current women and their methods of birth control that they are currently using, use optimally as real, everyday life people use them, what would be the predicted rate of pregnancy per 1,000 courses or however you want to express this. We know that methods fail, we know that.

That zero is not obtainable in this process short of females not taking this drug right now, but I mean best practices in normal settings, what would be the predicted rate of pregnancy in

this setting.

DR. MITCHELL: I think I can parse that question, to use an old term. One question is in efficacy in the normal use of the method, and, in fact, what our data suggests is that efficacy is better than normal data would suggest. We can spend a lot of time on defining on how best efficacy was defined some years ago.

In the population we have observed, what we see is roughly 1, 1.2 per 1,000. If all women were on the pill, I could actually get you some of those estimates, it's in the paper, but I think the real question is what is the efficacy if women are on two methods of contraception, which is what is specified in the risk management program.

The difficulty in assessing that is trying to find out whether women who report two methods were reporting two simultaneous methods. Those kinds of questions become extremely, not only invasive, but they become extremely difficult to ask, because you essentially have to understand if a woman is on the pill, did she take a pill every

day, if she was using the pill and the condom, did she use the condom with every act of sexual intercourse with the male partner.

One of the concerns is that women may be interpreting the two methods, may be using two methods, but forgetting the simultaneous. It is conceivable, this is sort of the law of unintended consequences that Dr. Trontell mentioned yesterday. A concern we have, although we don't have data to support it, is there going to be a fraction of women who say, okay, I have got to use two methods, I will use the pill a couple days a month and I will use the condom when I think of it.

I don't mean to dodge your question. We can give you contraceptive efficacy rates for any single method that was reported, and it's in the paper, in the New England Journal paper from '95, but we can't answer the question any more directly than that.

DR. GROSS: Dr. Kweder, do you want to comment on that?

DR. KWEDER: Yes, basically, it is similar

to what Allen had to say. We have some slides that display contraceptive method effectiveness rates as generally understood, but there really are not data that help us with the two methods simultaneously used, and Allen's point is exactly what we have struggled with, as well, does it mean, you know, how many women actually interpret use of two methods as simultaneous all the time. That, we don't know.

DR. GROSS: The next question is from Sarah Sellers.

DR. SELLERS: I am wondering if you have a regional distribution of the study participants.

DR. MITCHELL: We do, and it is compatible with the sales. I could get the slide out, I would be happy to provide you. It will take me a couple minutes to find it, but it is similar.

DR. SELLERS: Just one more follow-up, and we may have addressed this yesterday, but has the survey been validated at all with any medical records or exam data?

DR. MITCHELL: Specifically, how would

you--

DR. SELLERS: To confirm in particular any way to validate voluntary reporting on pregnancies. Primarily, that would be the only thing that we could look at.

DR. MITCHELL: I think the concern is false negatives, in other words, women who fail to report pregnancies, and we have not done that. That raises some privacy issues that are a little tricky to get around.

Pregnancies that are reported are followed up, and any pregnancy that is identified with any suggestions of malformations, the records are obtained if the woman will allow us to.

DR. TRONTELL: I would like to try and address Dr. Sellers' question. I just wanted to point one challenge in assessing pregnancy. Many health plans do not cover termination of pregnancy, so individuals who self-diagnose pregnancy and elect to terminate outside their usual medical care system will never be captured or ascertained.

DR. MITCHELL: Which is one of the reasons

that we rely on voluntary reporting from participants.

DR. GROSS: Thank you, Dr. Trontell.

Dr. Strom.

DR. STROM: I wanted to follow up on Dr. Kibbe's question with a comment and then a question to the company in follow-up. You were asking about the international experience in particular.

Anecdotally, my colleagues in other countries tell me that Accutane is seen as a uniquely American problem, but that is not because we are the only ones looking, but because we are the only ones using it so widely, that other countries don't use it anywhere nearly as widely as we use it, so use is much less.

What I wonder about from the company is whether you could give us sales data by population for some selected countries, so, for example, to try to nail down whether that anecdotal experience is correct, in other words, what is the rate of use in the U.S. population, how does that compare to perhaps the English population or the Swedish

population or otherwise.

DR. HUBER: We do not have the data on sales broken down by country here. That would take us a little time to compile and we don't keep those here in the U.S., so it would take us some time.

DR. STROM: But I think that is why you are not seeing the sensitivity from other countries.

DR. KIBBE: I think there is an underlying social issue, too, and that general acceptability of birth control methods in Sweden and some other countries in Europe are going to be quite a bit different than the United States. I am trying to figure out what factors are out of the direct control of the system that we have are impacting it, that's all.

DR. GROSS: Thank you, Dr. Kibbe.

Dr. Whitmore has the last question.

DR. WHITMORE: Can you clarify, you had a graph up there talking about the number of pregnancies during Accutane and then for the subsequent months after therapy, and I thought it

was 10 per 1,000 person years, is that correct?

DR. MITCHELL: It was about 9 during therapy, 9 per 1,000 during the course of therapy at that time.

DR. WHITMORE: So, just to clarify, that would be 1 in 100 essentially as opposed to 1 in 1,000.

DR. MITCHELL: Well, yes, but I am sorry, I accept your correction. I am confusing different--our usual rate estimators per course, per 1,000 courses, correct.

DR. WHITMORE: And that was person years, and therapy can range anywhere from 24 to 48 weeks depending how dosing is done essentially. I think that is a point that need to be re-emphasized as opposed to if birth control pills and a second form of contraception were used effectively, maybe more like 1 in 1,000 rate of pregnancy. I mean those numbers are not correct, but I think just to give us a ballpark idea.

One more question about your survey. There is incentive to fill out the survey. For

teenagers, their parents probably make them fill it out. For adults, there is a monetary reward for doing it, and also there are probably some adults who think oh, if I don't fill this out, something bad is going to happen, or think that it is part of all the program or something they need to do particularly with all the PR about Accutane and everything else.

So, I would say that a lot of people would probably fill out the survey, fill it out because of incentive reasons of some sort, and then I would ask you, these women are signing a form that says I will be abstinent or I will use two forms of contraception throughout therapy.

What makes you think that a non-anonymous survey is going to capture any information about people actually not doing these things, they have signed on a document saying they are going to do?

Also, reports about abortions, what makes you think that these women who have signed this document, if they do get an abortion, if they are not going to tell their doctor, what makes you

think they are going to report it to you?

DR. MITCHELL: Probably the fact that we are dealing with human beings would be a large part of that answer. We were similarly skeptical going in, and remain somewhat skeptical, but less so.

What is very interesting is how often we find women telling us things they have not told their doctor. In fact, we did--and, Dr. Katz, you had asked the question yesterday and I couldn't remember what it was when we bumped into each other, but it comes to mind now--and that question is really how accurately do the data reflect what the physician is doing.

We identified back in I think it was the early '90s, a group of women who reported to us that they had not had pregnancy testing prior to the prescription of Accutane. From their enrollment forms, we were able to identify the physicians who were in that loop.

We called those physicians' offices to ask sort of an anonymous survey question about we are just calling from Boston University, we are

querying physicians about their practices with respect to Accutane, and typically, very often the person responding would be an office manager or the office nurse rather than the physician.

We asked whether they routinely did, in fact, do pregnancy testing as one of a number of questions, and a surprising number--not a surprising number--a large number of physicians indicated that they routinely do pregnancy--I mean the office nurse said oh, we always do pregnancy testing, but a number of offices said to us we don't.

Now, would you expect a physician's office to tell a survey that they don't do pregnancy testing? The converse is also the case, that when we identify a woman who reports that she is sexually active and does not use contraception, we consider that woman at such great risk for pregnancy that the design of the survey calls for us to call that woman.

We call it reading the riot act. We call that woman and say to her that the behaviors you

reported to us put you at high risk for pregnancy, and we urge you to immediately call your physician, stop taking the drug. Incidentally, would you also be willing to allow us to talk to your doctor.

When the woman gives us permission to call her doctor, you would assume that the doctor would give you some response that would be compatible with what the woman is reporting, and, in fact, I can't give you the quantitative response, but there were a disturbing number of times where the physician would get on the phone with us, once the woman gave us permission, and would go to the medical record and read us from the medical record that the woman said she was actively--so here was a woman inviting us to find out, and what she was doing was telling the survey--this is a long answer to your question, but I think it deserves that--she was telling us something that she wouldn't tell the doctor.

So, the survey is actually in a position to find out things that a woman wouldn't tell the doctor.

DR. WHITMORE: I had no idea that you called patients. I think that is absolutely fantastic.

DR. GROSS: Dr. Mitchell, thank you very much for your presentation.

DR. MITCHELL: Thank you.

DR. GROSS: Dr. Katz.

DR. KATZ: I want to clarify. You call the doctor's office, and you said some said they didn't do any pregnancy testing, but you talked to the office manager and most doctors' offices--I happen to draw blood in the office, but most don't draw blood in the office--so, the office manager says no, we don't do pregnancy testing. They send them to the laboratory, but they don't do it.

DR. MITCHELL: First of all, let me explain this was a very biased sample. This was a sample of women, a small sample of women who had told us they had not gone through a compliant process, so we are already dealing with a subset that is hopefully small.

When we called--Dr. Katz, I can't remember

the specific questions, but we can get them for you--we asked a series of questions of someone who would be familiar with the offices practices, it often was the nurse, but it represents only a very small fraction, and we did incidentally try to reach those doctors subsequently and get them informed of what the appropriate practices were. I don't mean to suggest that was a widespread phenomena.

DR. GROSS: Thank you again, Dr. Mitchell.

We will now move on to Dr. Trontell, who had some information to present to us that will be helpful in our consideration of the questions.

DR. TRONTELL: There were some questions yesterday about the specifics of the clozapine program and also of the S.T.E.P.S. program. I am thankful to the representative from Celgene who came and provided information, which I will repeat, and I will also invite that individual to come to the microphone to supplement it.

But relative to the registration of patients in the S.T.E.P.S. program, patients are

registered by their Social Security number. In the event that that number is not unique, a second unique number is assigned to those individuals. So, the provision of patient anonymity in S.T.E.P.S. it isn't truthfully there. If you have their Social Security number, that can be readily linked to an individual's name.

The other question that was asked was about clozapine and the mechanism that led to its institution. In fact, information provided to me by one of the members of the Division of Neuropharmacologic Drug Products told me, in fact, that some of the experience that I cited with agranulocytosis related to post-marketing experience abroad where the product was marketed with recommended monitoring for white counts and prevention for agranulocytosis.

That rate was on the order of 1 to 2 percent, and that had been described in the era of the clozapine national registry in practice with mandatory monitoring of white count to be less than 1 percent, specifically 0.38 percent.

If there are additional questions, I would invite the individuals who know each of those registries to come to the microphone to address them.

DR. GROSS: Hearing none, we will move on now to Dr. Paul Seligman, Director of the Office of Pharmacoepidemiology and Statistical Science at the FDA, who will introduce the questions to us.

Introduction of Questions

DR. SELIGMAN: Good morning. I have been asked to present the issues and questions for consideration by the committee this morning and this afternoon.

Please note that these questions are part of the agenda that was distributed for the meeting and can be found after the agenda.

Before I begin, I just want to take a brief moment on behalf of myself and my colleagues at the FDA to also thank the members of the public this morning who were here to share their testimony and their personal experiences.

The issues and questions fall into the

following sort of broad categories. We are asking the committee today to evaluate the performance of the current program and the data that have been presented both yesterday and today, to consider options for improvement of this current risk management program, to consider how best to monitor any recommended changes, and to consider benchmarks for success as noted yesterday morning.

I think it was the first question out of the gate by Dr. Bigby, as well as others this morning, who have focused on how best to determine whether subsequent changes or any program that comes out of these deliberations should be determined to be successful.

[Slide.]

The first issue that we ask the committee to consider this morning is that based on the reports and patient surveys, there does not appear to be a meaningful decrease in the number of pregnancies reported in women taking a course of isotretinoin since implementation of the current risk management program.

We would ask you then to discuss the measurement and implementation factors that may have contributed to these findings.

[Slide.]

The second issue is based on prescription audits and patient surveys, use of the qualification sticker is high. Patient surveys suggest an inconsistent link between monthly pregnancy testing and use of the stickers. Reported pregnancies and patient surveys indicate incomplete or inadequate birth control measures among females.

Again, we ask you to please comment on measurement and implementation aspects of the current program that may have contributed to these findings.

[Slide.]

Question 3. FDA's goals for the Isotretinoin Pregnancy Prevention Risk Management Program are that: no woman who is already pregnant be prescribed and dispensed isotretinoin, and that no pregnancies should occur while on this therapy,

and that effective pregnancy prevention occur throughout the course of treatment.

[Slide.]

In recommending any changes to the risk management program, we ask the committee to consider the potential tools and strategies in light of the likelihood of effectiveness in further reducing fetal exposure, the practical impact on health care providers who prescribe and dispense the product, and the impact on patients who must navigate any such program.

[Slide.]

Given these factors, we are asking the committee to consider the following options:

(a) Continue the current risk management program without additional tools, and if this is the recommendation, if so, what approaches do you recommend to improve adherence with the program by patients, physicians, pharmacists and others, such as health educators?

[Slide.]

(b) Or to consider modification of the

current program with additional risk management tools to reduce fetal exposure.

We list a number of them here, such as programs to enhance education and interaction with patients to identify and minimize high risk behaviors; to tighten the linkage of prescriptions dispensed by pharmacists with required check of pregnancy test results; the registration of patients, pharmacists, physicians and/or others such as health educators; limiting the access or distribution of the drug, or other tools. In recommending the other tools, we would ask you to describe them.

I should note that in the course of our discussions and deliberations, other tools have also been mentioned, but not listed here.

[Slide.]

Question 4. In order to adequately monitor the risk management program, we ask the following:

(a) Would it improve monitoring of risk management program performance to register

patients, pharmacists, physicians, and other relevant participants?

(b) If participants in such a risk management program are registered, how can this be more effectively done in a multi-source environment, so that individuals are not registered multiple times or double-counted?

[Slide.]

Finally, we are asking the committee to identify critical benchmarks for determining the success or failure of the pregnancy risk management program, and suggest, for example, such as reducing to zero the number of women who are pregnant at the initiation of isotretinoin treatment, and others.

I am happy to answer any questions about these issues and provide any clarification as need be.

DR. GROSS: Thank you, Dr. Seligman.

Committee Discussion

As Chair, I am going to make a suggestion that we consider Question 3 last because that is

the recommendation of the committees on what the program should be in the future.

Question 4, I suggest be considered before 3 because it talks about whether or not registers would be helpful, and that may be part of the ultimate plan that we come up with in Question 3, and assessing success and failure is something that we can also consider beforehand.

Is that okay with the committee if we do it in that order, Question 1, 2, 4, 5, then 3? Does anybody have any objections to that? Okay.

Why don't we begin with Question No. 1. Based on the reports and patient surveys, there does not appear to be a meaningful decrease in the number of pregnancies reported in women taking a course of isotretinoin since implementation of the current risk management program.

Data has been presented on that. Please discuss measurement and implementation factors that may have contributed to these findings. If I may be so bold as to say that insufficient data has been presented to answer that part of the question,

but let's hear what committee members think on those issues.

Dr. Gardner.

DR. GARDNER: As a non-clinician, it would help me greatly to understand what happens in the clinician's office in terms of the implementation of these processes both from the standpoint of physician and patient burden, and also the logistics we heard yesterday, a scenario of trying to get a pregnancy test, is it the result or a new request, and so on.

Could the clinicians comment on how these processes are implemented in practice for example?

DR. GROSS: Any dermatologist want to--Dr. Katz.

DR. KATZ: We will walk you through it from the beginning. First of all, the patient has been seen multiple times previously, on every other treatment we know, different antibiotics starting with the least risk of inducing and most used for decades, and then antibiotics with a high risk profile.

Then, the patient is evaluated, and if it is a minor, the parent is in the office initially, a complete discussion of all side effects are done, and then the female patient, one can't portray in this meeting the doctor-patient contact and the validity of patient response, reliability of patient, we can't project that here, but the physician assesses that, as well.

Then, you give the patient a choice of having a parent leave the room, so you can discuss the contraception end. We ask them if they are using contraceptives, and it is burdensome going through this entire thing, then, of all the side effects involved.

All risks are mentioned and if it is decided to go ahead with the Accutane, in female patients, baseline bloodwork is done, CBC, hepatic profile, lipids, and HCG pregnancy test, and they are told to come back at the time of the next period for another pregnancy test, or they can get that done, since they are not coming, that might be in 10 days, they wouldn't have to come back to the

office, they can go to the lab and get the laboratory test. They will often fax it, and then they can come by and get a prescription with the yellow stickers.

They are told to come back in two weeks and then every four weeks through the course of treatment. Bloodwork is obtained each time, and then they are given a prescription again. They are reminded each time about the necessity of two means of pregnancy.

They are asked about the side effects, how they are feeling as far as generally, and once again you can't project everything. You are looking at their face to see how they are doing. With all this said and done, you remind the patient each time about the necessity of two means of contraception.

A lot of times people say yes, it happened to me, to bear on this question further, how can these adverse effects be reduced, it can't be to zero because a patient says that she is not sexually active, and each time she remarks a little

bit, she said I told you that last time, and each time I remind her, she reminds me that, doctor, I told you I am not sexually active, and then two weeks later she calls me and says she missed her period. This happens. So, how do you eliminate that?

Now, it so happens, then, we got a pregnancy test, she wasn't pregnant, she had just missed a period. But she was concerned because obviously, she wasn't sexually inactive. So, these are the problems that face us, and that is why this is going to happen anyway.

Does that answer your question?

DR. GARDNER: Thank you.

DR. GROSS: Dr. Crawford has a question.

DR. CRAWFORD: A follow-up either to Dr. Katz or any other member of the committee. Other than actual pregnancy testing, what would be different with the male patient prescribed isotretinoin?

DR. KATZ: No, except that contraception isn't discussed, which might bring up some points

that came up with the male patients, but, no, that is not discussed.

DR. GROSS: That is an issue we will need to consider later on, whether male contraception should be recommended.

At this point, I would like to encourage the committees to specifically stick to the question.

The first part of the Question 1, does anybody disagree with the statement, the statement being there does not appear to be a meaningful decrease in the number of pregnancies? Does anybody disagree with that? Yes.

DR. BERGFELD: I would like to speak to that. This was a new program, the S.M.A.R.T. program for the dermatologists, and when they were asked to participate, the American Academy of Dermatology put in place very intensive teaching courses at all of their meetings to inform the dermatologists of their behaviors.

We were also visited by the company in our offices in which the S.M.A.R.T. programs were

introduced to us. We then had didactic sessions to go through what our responsibilities were to be in this program, and we were requested, and it was inferred, that unless we signed up, we would not be prescribing this drug and that we would be out of order to prescribe this drug.

So, in my practice at the Cleveland Clinic, we did abide by what we felt was the best thing for our patients, we became informed, we abided by the sticker qualifications, and we did somewhat what you did, Dr. Katz. We used the forms that are given to us to go over with the patients.

But what I would like to say about this is that what happened was that the compliance of the dermatologists went up with informed consent and education of the patient.

I think that is reflected by the fact that you have decreased numbers of prescriptions being written overall, but a constant number of pregnancies, and I think there has just been an increased reporting that has gone on because of the educational program.

I think when you open or begin a new program, this is what you would expect, and I would think that what we here do today would be to enhance this program to make it more efficient and improve it, so the reporting continues and the education continues, with the ultimate objective to reduce the pregnancies to zero if possible.

DR. GROSS: Okay. I am still trying to answer Question No. 1. Let me take the prerogative of the Chair and say there does not appear to be a meaningful decrease in the number of pregnancies.

Would anybody disagree with that? Dr. Whitmore.

DR. WHITMORE: The one thing that you asked was are there contributing factors.

DR. GROSS: That is the second part of the question. Let's do the first part first. Otherwise, we are never going to get through the day.

Does anybody disagree? Dr. Ringel.

DR. RINGEL: I think the real honest answer is that we really don't know. We don't know

if Dr. Bergfeld's comment about the number being artificially high because of increased reporting is true.

On the other hand, if that number really reflects the actual rate, that is problematic because the rate should have decreased, in fact, because there were decreased numbers of prescriptions written.

I think the only thing that this shows is we don't have the answer to that, and we really need a registry.

DR. GROSS: So, we have one dissenter. Does anybody else dissent on the statement there does not appear to be a meaningful decrease in the number of pregnancies? Dr. Bigby.

DR. BIGBY: The suggestion has been raised should we consider as an objective, the rate or the absolute number, so if, in fact, you could show, and you could probably do this, that the rate had actually decreased and the absolute numbers in the hundreds, is that a success. That is the point I think we should think about, so maybe rate isn't

what we should be looking at.

DR. GROSS: Could I see a show of hands on the question there does not appear to be a meaningful decrease in the number of pregnancies? We are never going to get through the program. We are going to be stuck on Question 1 until 5:00 p.m. To me, the answer seems obvious. Yes.

DR. SCHMIDT: Yesterday, on page 70 in this Pregnancy Rate and Accutane Survey, this, I thought was meaningful that it decreased, that there was almost like a 2- to 4-fold decrease in some of the slides that were shown in the decrease in pregnancy rate.

I want to add one other thing to back up Wilma. You know, people are very, very anal about doing these different things in the offices.

At least in Houston, I mean we really bend over backwards to do everything and cross out t's and dot our i's on these, and from a clinical experience, I took a straw vote at one of our major meetings, our Thursday morning conference, and since this S.M.A.R.T. program started, I could only

identify in this group one pregnancy that had occurred at least in our group, which probably includes a lot of people doing a lot of Accutane.

DR. STROM: To bring it to resolution, I think the problem is an issue of terminology and people are confusing numbers and rates. The question is there does not appear to be a meaningful decrease in the number of pregnancies reported. I think it is very clear that is the case. That is based on spontaneous reports, the numbers are roughly even.

All of the issues everybody is raising are correct in terms of issues of reporting that maybe that the rates have gone down despite the fact that the numbers haven't, and I think those are the two things that people have confused.

But the question says not a meaningful decrease in the numbers, and those numbers are based on spontaneous reports, that is clearly the case. The numbers are roughly the same.

MR. LEVIN: I just want to add to Brian's comment that I think what people are responding to

is the second part. I mean the issue of whether we are seeing better reporting, more accurate reporting or actually that things are remaining the same is a question of measurement, and that is in the second part of the question.

DR. GROSS: So, a show of hands on the first part of the question.

DR. DAY: Excuse me. Could I ask a clarification? I know these questions have been set for some time, but is there a way for us to ever modify it, so that we could have a second part that we could vote that the number has not decreased, but that we do not have sufficient evidence about the rate or the rate has or has not? Can we address number and rate in this question? Otherwise, some of us will be uncomfortable in voting quickly one way or another to get it off our agenda.

DR. GROSS: Sure, there is no reason. I think we should answer the question, then, if you want to put another statement, there is no reason we can't do that.

DR. TRONTELL: May I offer some clarification from the Agency? We do our best to express the questions clearly, but our intent in this question was, in fact, to engage the committee is some discussion on the issue of ascertainment of pregnancy, some of which have already been raised in some of the remarks around the table.

We would appreciate some discussion or closure around it, not so much an issue of debating whether or not the numbers have changed. We can make our assessment of that, but the issue of ascertainment, as well as implementation are what we would like the committee to address.

DR. GROSS: So, ascertainment really relates to the second part of the question.

A show of hands on the number of pregnancies. Do all people think the number of pregnancies appear not to have decreased meaningfully? A show of hands that they agree that is the case.

[Show of hands.]

DR. GROSS: Those who disagree?

DR. KIBBE: Abstentions? I think the data is inconclusive and I will not vote one way or the other when the date is unreliable.

DR. GROSS: Fine. So, the majority agree and there is one abstention.

DR. KWEDER: Dr. Gross, if there is a vote, we would appreciate it if you could record it for the record in the instances when you do vote. Thank you.

DR. GROSS: For the record, the group agrees there does not appear to be a meaningful decrease.

Do you want to go around the room, is that what you mean by record?

MS. TOPPER: For the record, we are required to go around the room individually and have each person record their vote. If you will say your name and you agree or disagree, we will need to have that. Thank you.

DR. GROSS: Art, do you want to start?

MR. LEVIN: Arthur Levin. I agree.

DR. SAWADA: Kathy Sawada. I agree.

DR. VENITZ: Jurgen Venitz. I agree.

DR. STROM: Brian Strom. I agree.

DR. BERGFELD: Wilma Bergfeld. I agree with the number, but I do not agree with the rate. I believe the rate has gone down.

DR. GROSS: You believe the rate has gone up?

DR. BERGFELD: Down.

DR. RAIMER: Sharon Raimer. I am going to abstain. I don't think we have good enough data.

DR. GROSS: So, that is an abstention?

DR. RAIMER: Abstention.

MS. KNUDSON: Paula Knudson. I agree.

DR. BIGBY: Michael Bigby. I agree with the statement that there hasn't been a meaningful decrease in the number of pregnancies reported. I do think that there is information that the actual rate has decreased.

DR. HONEIN: Peggy Honein. I agree.

DR. COHEN: Michael Cohen. I agree.

DR. WHITMORE: Beth Whitmore. I agree there has not been a meaningful decrease.

MS. SHAPIRO: Robyn Shapiro. I agree and also observe that by asking for numbers as opposed to rates, there seems to be an implied goal about what we should be looking for, whether intended or not.

DR. EPPS: Roselyn Epps. I agree.

DR. SCHMIDT: Jimmy Schmidt. I agree.

DR. CRAWFORD: Stephanie Crawford. I agree there has not been a meaningful decrease in the absolute number.

DR. GROSS: Peter Gross. I agree.

DR. WILKERSON: Michael Wilkerson. I agree with the question.

DR. RINGEL: Eileen Ringel. I agree also.

DR. VEGA: Amarilys Vega. I think that we don't have sufficient data.

DR. GROSS: So, that is an abstention?

DR. VEGA: Yes, sir.

DR. DAY: Ruth Day. I agree with the decrease in number reported and make no claims about anything else, numbers that may have occurred, as well as changes in rate.

DR. KIBBE: Arthur Kibbe. I abstain on the basis that the data is not conclusive, nor is this an appropriate question.

DR. GARDNER: Jackie Gardner. I agree.

DR. KATZ: Robert Katz. I agree.

DR. SELLERS: Sarah Sellers. I agree.

DR. GROSS: Thank you all.

Now, for the more difficult part--that was easy, believe it or not--please discuss measurement and implementation factors. This is really where the expertise of the committee could be enormously helpful.

Any suggestions, comments?

Robyn Shapiro.

MS. SHAPIRO: I agree with your earlier comment that there is insufficient data to weigh in on that.

DR. GROSS: Anyone else? Art.

MR. LEVIN: I guess I am just confused by what the rate, when talking about rates, where we are. If I look at P70 of the Roche presentation, which is sourced at Slone and tracks the number of

pregnancies per 1,000 Accutane treatment courses and the number of pregnancies per 1,000 patients per year, there does seem to be a decrease, but where we get down to is around the number 3, and we have just heard from 4 to 3. Over the period of 1989 to the year 2002, and if we sort of track into, you know, sort of approximate on this graph where the first prevention program came into effect and then where S.M.A.R.T. came into effect, which is probably not on this graph actually. You know, we see recent history.

But we just heard of a rate of 1, I think, in the presentation from Slone. So, I am just personally somewhat confused as to the different presentations of what the rate issue is, whether it is in the course of treatment or per patient year what we are discussing here.

DR. GROSS: Sarah.

DR. SELLERS: I would just like to remind everyone that we are talking about a reporting rate, we are not talking about an incidence rate, and the primary objective of the risk management

program is to decrease the number of pregnancies, not to decrease the reporting rate.

These are reported pregnancies and the number of reported cases are small in comparison to what we believe are the overall number of pregnancies that may be occurring and exposures during pregnancy.

So, a meaningful decrease in a reporting rate, in my opinion, has very little validity in the discussion of decreasing pregnancy exposures.

DR. GROSS: Thank you.

So far we have been talking about measurement on this question. How about implementation factors, implementation factors that may have contributed to a lack of a decrease in the number of pregnancies? Dr. Katz.

DR. KATZ: Just to take one second to reiterate an anecdote--I won't reiterate it--but to remind you we don't have part of not being able to improve on it although we have to keep trying and use every effort is the human fallibility and that was my only point in mentioning that little

anecdote. You can't completely control human behavior, nor can we unfortunately 100 percent control physician behavior and how much time somebody is spending with a patient, and so forth.

So, some of it, we are not going to be able to reduce it to zero.

DR. GROSS: A point well taken.

DR. KATZ: It was also pointed out yesterday, with all the stringent requirements that one might consider adding, that still doesn't eliminate pregnancies. It will capture the numbers better and it may be a reminder, an education reminder, but if somebody is going to tell the doctor that they are sexually inactive, you can't force them to take birth control pills. There is a certain limit to what we can do.

DR. GROSS: Exactly. There is going to be a limit to what we can do, but does that mean we shouldn't try to make the program stricter. I mean that is going to be one of the things we have to consider.

Dr. Venitz has a comment?

DR. VENITZ: Yes. My comment is with those survey instruments in general. We just had a preview I think of our discussion when we looked at the reported numbers, and you stated that we are dealing with reported numbers.

I would make the observation that in my mind, the only number that has any validity is the fact that 28.2 percent of the patients participated in the survey, which means the remainder, 70-plus percent did not participate in the survey.

We are looking at pregnancies, which is an event that presumably is rare with or without the implementation or the appropriate implementation of a prevention program, so we are looking at in my mind bias, at least potentially biased survey sample.

So, any of the numbers that follow from that point on, to me, cannot be interpreted whether they are made or reported, they do not reflect any interventional effects. So, the observation I am making is one of the limitations and anything that I have heard over the past day and a half is the

fact that only 28 percent of the patients post-S.M.A.R.T. participate in the survey. So, all the numbers from that point on, to me are meaningless.

DR. GROSS: An important point.

Dr. Strom.

DR. STROM: I would like to address the measurement issues and to limit it, to some degree this may be duplicative and I think is expressing what everybody is saying, and then move on to the implementation factors.

For a measurement issue, I think to a large degree we are looking at spontaneous reporting data. The problem there is we have an incomplete numerator, we have an incomplete denominator, and given that, we can say something about numbers.

In this case, the numbers are unusually important perhaps because they are telling us there are still people being affected, but we can say nothing about the rates, you can't calculate rates based on spontaneous reporting data.

You have got again uncertain numerators

and uncertain denominators. I think the only place we have rates are the survey data, but as Dr. Venitz said, and as Dr. Mitchell has talked about, as well, there are obviously limitations that have been well recognized in the survey, and as much as it could be designed to address it, it has, but it is an intrinsic problem when you are dealing with a voluntary system, and the enrollment is voluntary accordingly.

In terms of implementation factors, I think what we are hearing is an extraordinarily complex system that it was certainly hard for us to be explained to us, no less harder yet for clinicians to implement. I am a general internist, not a dermatologist, so I don't prescribe Accutane, and I haven't been subject to it, and the more details I hear about it, the gladder I am to that effect.

I think there is a very substantial burden here on physician and on pharmacist. I think there is an enormous obviously lack of reporting as we talked about, and I think there is a huge lack of

ability to enforce I think is the key issue.

I think to the degree we are talking about a system where you are trying to drive things towards zero. You will never achieve zero for the reasons everybody is saying, but we are trying to drive it towards zero.

You are not going to be able to get this complex health care system with all of the enormous heterogeneity and hundreds of thousands of providers when you are dealing with physicians and pharmacists, and try to ask the health care system to enforce it in a voluntary way.

It is just never going to happen, and I think as long as we are relying on a voluntary system in terms of the implementation, we can't expect it to go as low as it can.

I am struck and impressed by how well it has done given all of that. I think there has been enormous compliance on pharmacy part, I think there is enormous compliance on dermatologists' part.

I think the answer isn't to keep hitting people on the head, because we can't expect more

from a voluntary system than we have already gotten. I think the problem is the implementation has been voluntary and has been diffuse, and has been totally decentralized.

DR. GROSS: So, zero is a laudable goal and we can try to design a program to reach that goal, but not expect that we will ever get there.

Dr. Vega.

DR. VEGA: I just want to concur with Dr. Strom, that in terms of the implementation factors, I think that the weakest of the links here is the voluntary nature of this program, as he so nicely described. I think that is the best we can get from this type of voluntary program.

DR. GROSS: Dr. Epps.

DR. EPPS: Just a few things I wanted to say. Although I know this is a risk management, part of the risk-benefit ratio, also to say something about the benefits, and that it does benefit a lot of patients, and those of us who use it or some of us who may have taken it, I feel that I should say something for them, because I think it

is a very useful drug, I think it is a very important drug.

Dermatologists, in general, are not very cavalier about prescribing it. Most of us are very careful. I have treated a lot of minor patients or young people, and if either the parent or the child does not agree, you just don't give it.

If the child is involved in risk-taking behavior, they are the ones that are smoking and underage drinking, they are probably having unprotected sex, you don't give it to them. So, patient selection is also very important.

Dermatologists, in general, quite a few are solo practitioners, kind of an independent group, and to get over 90 percent participation, anything isn't a miracle.

Also, I agree with Dr. Katz, it is very difficult to control for human behavior or for human biology, and there are some patients who will say or do, your history is only as reliable as your informant, and you have to, you know, you take what your patient says, you can look for signals for

other things.

When we deal with minors, however, certainly you have to involve the parent and get their consent. With adults, you can't control adult behavior. You can make recommendations, you can make suggestions, but we don't go home with them and we can't control. We can advise, and we can withdraw the medication if they aren't doing what they are supposed to do.

There have been questions about international patients. I guess it should be said that different ethnicities have different experiences with acne. It is not the same in all cultures. Some cultures are more severe than other people, so I am not sure the emphasis on other countries is that meaningful.

Also, if the survey is voluntary and complete, it doesn't mean that it is necessarily truthful. A couple of questions might need modification for minors, such as did you sign the consent. Well, a concrete young person might say no, I didn't, my mother did, but I didn't sign the

consent, so you might want to say did you or your guardian or parent do X, Y, or Z.

There are times when we do talk to parents confidentially if they have something to say or give the prescription, so the young person filling out a survey may not know that there is a sticker involved.

So, there may be a few little modifications that could be done on the survey, as well.

DR. GROSS: I have a question of Dr. Epps. Would you like to make some suggestions? You brought up the issue of selecting the patients who you think would be appropriate rather than just accepting whether they say yes, I will comply. This might be helpful in designing a plan to particularly say maybe this person is not appropriate assuming they have cystic acne.

DR. EPPS: Well, as has been alluded to earlier, the doctor-patient relationship is extremely important. I mean it is pretty unusual to give, unless it's a male, to give Accutane on

the first visit. I mean it is not usually done. You need blood tests, you need follow-up, you need consents.

As a subspecialist, I have sometimes referred patients who already had treatments. They come with a reference from their physician. I usually talk to them or I might have medical records from the referring physician indicating what medicines they have had and how long they have had them, but still you are still going through consent, you are still giving out the bound spiral notebook folder, and proceeding in that way.

A lot of times--I guess part of my pediatric background--you talk to the young people and ask them, well how is school, well, you know, I skip and I don't go all the time or I am not in school right now. I mean it is probably not a good person.

Multiple visits are helpful because you will know whether they come back or whether they are compliant. If they come back with half a vial of pills, then, that is probably not a good

Accutane patient.

I know some of us have been talking about pills and people who have them left over and people who share, and that is always a concern, too, and some of that is timing of appointments.

You tell them take all of your pills, you know, and sometimes it requires a follow-up after the end of course, not only whether you are monitoring blood tests, but to find out how they are doing.

You can't repeat the Accutane course for two weeks anyway--not two weeks, two months--if you need to repeat a course. Most of them don't need it, but they sometimes do like to follow-up with questions or concerns.

I think most people are trying to do the right thing. That is what I would like to emphasize, and I think most patients are trying to do the right thing, I really do.

DR. GROSS: Dr. Schmidt.

DR. SCHMIDT: I pass. Dr. Epps said everything that I wanted to say.

DR. GROSS: Wonderful.

Dr. Sawada.

DR. SAWADA: I just wanted to get back to Dr. Venitz's and Dr. Strom's comments. I would certainly agree with them that from the outset yesterday, getting the information and the numbers and the wonderful slides, et cetera, it became inherently confusing as to how valid the basic numbers were.

Certainly, I think that things contributing to this confusion with the validity of the numbers obtained has to do with the voluntary nature of the survey. I certainly think that is something that we have to discuss.

The other thing is the recall nature of the survey, as well. I know that if I don't dictate in the first 24 hours of seeing a patient, if I have to wait 24 hours, that information is lost. It may just because I am--no offense to seniors--but it may just be that I am advancing myself in age, but I certainly would suggest that something other than recalling nature of the survey

is something to consider.

The other thing is contacting the physician. I have never been contacted or informed that a patient has filled out any of my surveys. I certainly think something has to be done to protect the privacy of the patient when we review those records, but that would at least be able to give you a corollary between what is in my record and what the patient says.

DR. GROSS: Dr. Wilkerson.

DR. WILKERSON: A couple of comments. We have a saying in Texas you can lead the horse to water, but you can't make him drink. That certainly applies to trying to legislate or trying to force people into compliant behavior, so whether we make these requirements mandatory or not, there is nothing that prevents that person from putting untruthful answers on a document that they send back to an anonymous third party, no more than it prevents them from making false statements to their physicians. Patients tend to respond to your expectations and I think they feel very bad when

they do fail.

Sixty percent, I was surprised that that was the goal that was set. If anyone has ever done measurement in population satisfaction surveys, whatever, 60 percent is a lofty goal. Generally, if you can get 10 percent back on a voluntary survey of any type, I am told by industry is very good, and sometimes even 1 percent.

So, to see that we are getting over 20 percent return is certainly quite amazing, particularly when we are looking at the intimate details that patients are revealing about themselves. We are thinking about these details in a clinical sense, but to the patients revealing this, this is like taking their clothes off in public almost.

My other question about this is from the data, which I didn't see, is do we have particular physicians who are non-compliant and result in an overly large number of represented pregnancies. This is an issue that we don't like to deal with.

We know that there are good drivers and

bad drivers, and certain people seem to have accidents more than others do, but certainly every one is, because the risk of probabilities expose the potential of having an Accutane-exposed pregnancy no matter now good a job they do, but certainly we need to look at practitioners also in terms of are some people over-represented and why are they over-represented.

The other comment I had was I thought that the survey forms that I saw was the first time I had had an opportunity to see those documents that I could recall, I thought they were incredibly complex and written well above what I would expect for the average patient.

I had to sit there and read through the questions a couple times sometimes to try to grasp. I think we need a simpler, shorter document.

DR. GROSS: Well spoken. I think the data presented to us at least really showed a paucity of risk factors that would help us deal with failed implementation, and hopefully, future surveys will include more obvious, not so obvious risk factors.

The next questioner is Dr. Honein.

DR. HONEIN: I think one implementation factor that may have decreased the effectiveness of the current risk management plan is the existence of multiple names of this program and multiple brochures and multiple surveys, which I think is very confusing to patients and likely decreased participation in the survey, or conversely, we don't know how many patients enrolled in both surveys, because there is no information going to the patients to even tell them that they shouldn't enroll in the second survey.

I assume the vast majority of prescribers got the S.M.A.R.T. materials from Roche because that came out first, and unless they got a very small supply, they probably didn't have to request the other materials, but we saw yesterday that now over half the prescriptions are for the generics, so when they are getting their medication, they are getting a different information, a different enrollment form.

I think unifying this into one approach

would help the situation a lot.

DR. GROSS: Good point.

The next question comes from Dr. Bigby.

DR. BIGBY: I think that the major problem with this medication is that it is uniquely and highly effective for treating nodular acne, and I think for most dermatologists, it is a drug that is very important for us to be able to take care of patients, but it also is teratogenic and therefore I think that the fact that we are talking about making decisions about rates on the basis of spontaneous reports and utilization really is something that--I think we are remiss in having to rely on such a paucity of data in trying to make decisions.

I think one of the things that has to be accomplished is that we make a mechanism where we will actually detract female patients who are taking the drug and make a really good effort to make sure that we learn the outcome of those patients while they are on the drug and for sometime after.

I think only that way can we start to have accurate measurements about basically what the rate is and what effects interventions have.

In terms of implementation factors, one of the things that struck me is that, you know, I see patients at a university health service twice a week, and the sort of demand for Accutane is extremely high. Obviously that age group patient is one that is at high risk for becoming pregnant.

One of the things that I try to make sure is that patients are at least on one effective form of contraception, and I think it is very well known and published in a book "Contraceptive Technology," what are the effective forms of birth control in actual use. I mean they are basically sterilization and hormonal therapy, and that the failure rate of just about everything else is unacceptably high for this drug.

So, one thing that we can do is to make sure that people are at least on one effective form of contraception, and then I would just like to make a sort of comment about the abstinence

loophole, I like to call it.

Someone said, well, if a patient insists that they are abstinent, you can't make them take the pill. Well, yes, you can. You can give them the choice of either use an effective form of contraception or not give them Accutane.

It always puzzled me about, you know, abstinence as a loophole because if abstinence is your primary form of contraception, what is the secondary form.

So, if are abstinent on the pill, that works for me. But if you are abstinent and your secondary form of contraception is a condom, then, it makes no sense whatsoever, because once you have to use a condom, you are not abstinent anymore, and a condom by itself is not an effective form of contraception.

You know, the sort of published efficacy of condom alone is extremely low. Condom and foam gets to be I think around failure rates of 1 percent, but condoms alone, I think the pregnancy rate is as high as 10 percent in use.

So, I think that we should eliminate the abstinence loophole and make sure that all patients are at least on one effective form of contraception, and then we can talk to them all we want about using two simultaneous forms of contraception, but I think we can at least start with them being on at least one effective form of contraception.

DR. GROSS: Thank you for your comments on the twists and turns and human logic.

Would anyone like to comment on whether or not the survey in the future program should be mandatory? Dr. Cohen.

DR. COHEN: I think it should be mandatory. Yesterday and today, I think especially with the patient survey, I guess, several of us remarked about how little we know about the actual causes. I know I did yesterday, and I think you did, Peter, as well, and others.

To me, not only should it be mandatory, but I think particularly with any follow-up that is done with patients that became pregnant, where the

failures were, we really have to spend time asking questions about what actually went wrong.

To me, that is absolutely critical, and sooner or later, you would be able to put together some data that would be of tremendous help in the future in reducing these failures. So, to me, that would be critical, a different design, at least with the follow-up that is done, and then tracking what those reasons are.

DR. GROSS: Dr. Crawford.

DR. CRAWFORD: Thank you. I wish to expand upon what both our Chair and Dr. Cohen just said, and it is also follow-up to the first question I asked yesterday. One, I do think surveys should be a mandatory part of the risk management program, but I think they must be coupled with some type of failure mode effects analysis.

In response to different ways of saying how it was handled, to my recollection, yesterday, Dr. Huber stated that Roche had some follow-up steps based on the S.T.E.P.S. and the S.M.A.R.T.

program.

Dr. Mitchell described some follow-up with their survey processes this morning that included, with permission of the patient, talking with the physicians and comparing some of that data.

Dr. Miller gave two case reports. One of the speakers from the open hearing, of course, that is another case report, but that was a different risk factor that was brought up that hadn't been put on the table before.

So, I think part of the risk management program, in addition to the survey, that we really should strongly suggest the need for more formalized follow-up of the failure cases including qualitative data, not simply asking what went wrong, but truly doing histories in cases, because the patients may not know what went wrong. We have to ask questions beyond what could just be checked off, really hear their descriptions of everything that happens.

DR. GROSS: Thank you.

Dr. Ringel.

DR. RINGEL: I was going to address specific parts of the program that were implemented that could have contributed to the number of pregnancies, and I think one of those was the stickers. The stickers are a surrogate, and I think that the FDA has shown very clearly that they correlated very poorly with the pregnancy testing, but that is not all they did poorly.

Supposedly, those stickers, there was a lot in those small stickers. Supposedly, those stickers meant that your patient had the pregnancy test, it meant that they had the pregnancy test during menses, which, of course, you have no way of knowing.

It means that you had made sure they were going to be on two forms of birth control, that you had educated them, that you have done the consents, and that they had been on birth control for a full month. That is a lot for a little yellow sticker to do, and I don't think it did it very well. It didn't even do the one thing it was really supposed to do, which was to correlate with pregnancy

testing.

So, I would suggest that we do one of two things, either just get rid of the stickers and get the pregnancy tests faxed to the pharmacy, so they will know that they are really there and they have really been done, or make those stickers mean something.

In other words, make them into a checklist, so the doctor actually has to say yes, they have been on birth control for a month, because I know it has been a month since I last saw them and I got in touch with the gynecologist, yes, I did the consents, you know, yes, I did the pregnancy testing, and at least let them check off that they have done the things that they have done, so it has some meaning. At least it will be a reminder, if nothing else, or just get rid of them.

DR. CRAWFORD: Dr. Gross temporarily has stepped out, so again, I get to say I have got the power.

Dr. Day.

DR. DAY: A lot has been said so far and

will continue to be said about human behavior, and I think the problems with human behavior should be pointed in all directions. To be human is to err, and there are errors that happen along the way from the physician's office, the pharmacist, the patient, and so on.

Very often, for example, in the physician's office, the affixing of the sticker is an interesting question. What happens if the patient comes in and needs to get the refill, and the physician is with another patient or out of town, does anyone else in the office have authority to apply the sticker, such as the office nurse or administrator, and what they might do is go and look in the chart and say, oh, yes, this patient has been qualified by the doctor.

That was sometime ago, and if that person then doesn't know that there has to be a requalification procedure every single time, that person might say, on, here is your sticker, go to the pharmacy.

So, we could generate many, many

opportunities for human error to happen along the way. But to focus on the patients, I think we have confounded human behavior with some other things, and one of the most important things is comprehension.

To my knowledge, there has not been comprehension testing provided in the survey materials. There is questions did you do this, and so on, and so forth, and do you understand that, and then it tells you what you are supposed to understand. Of course, you say yes.

So, I think that there is a confound when someone doesn't do something, is it because they don't know that they are supposed to do it, or is it because they know but either they choose or forget or circumstances get in the way of them doing the thing.

A colleague here reminded me yesterday about the speed limit. We all know that the speed limit might by 65 miles an hour in a certain area, but not everyone goes 65 miles an hour, some people go faster.

So, we have this confound of comprehension and behavior, but it is not insoluble. Currently, at Duke University, we have a government-funded project on studying comprehension of the information to patients in the Medication Guide for Accutane.

So, it may well be when the results are in that the comprehension level is high and therefore it is a behavioral problem, and interventions need to be addressed there, or if the comprehension level is low in some aspects, but not others, then, additional materials or education or something needs to be addressed to those points.

So, I don't think we should throw up our hands about human behavior, and so forth. It can always be, if you will pardon the expression, more better, but we have to understand why there are failures, not only of the failure effects approach, and so on, but is it comprehension or is it behavior, and a relative blend of those, and how do those interact.

So, I am sorry our Chair is absent while I

put forward this plea to de-confound the many important aspects that go into behavior that is not fully appropriate.

DR. CRAWFORD: Thank you.

Dr. Schmidt.

DR. SCHMIDT: I think we need to magnify our certainties, and one of the certainties is that people, when they just listen to one person or they look at one page, are not going to pick up the information.

At least I and my colleagues in Houston usually have people go to the gynecologist and get a consultation for their birth control if they are in a risk population, and then the other thing I want to address is I don't want to put all my patients on birth control pills.

I really have young girls who are genuinely abstinent, and I do not want to put them at risk for retinal hemorrhage, and I truly believe when they come in with their mother that they are abstinent.

Now, human nature being what it is, there

is a wonderful word in a prescription called Prevent, and I always tell my patients that if they have unprotected sex, and I have had them call, I will give them a prescription for Prevent to take, the morning after pill. I think this is something that needs to be mentioned.

DR. GROSS: Robyn Shapiro, did you have a comment?

MS. SHAPIRO: I am going to respond to what I think you wanted us to talk about, and that was the surveys. This plays on Ruth's point a bit.

I think that when we look at some of the proposals in the packages about the interaction with the program, and I am not so sure what that means, but I have an idea about maybe what it could mean, and that is, before the first prescription is written, that there be a check of understanding about what is supposed to happen in that informed consent process.

If there is a failure and/or depending on what the survey says, there is an indication of intent to engage in risky behavior even with

understanding, that that be looped back to the prescriber, who then who would have to readdress whatever the problem in understanding or intention is with the potential patient, and that then the prescriber loop back to the program to confirm that yes, in fact, we cleared this up and therefore, as a substitute for a sticker, rather direct communication from the prescriber to the program, which would go to I guess the pharmacy, that there be a check on assurance of understanding and intent to comply, and that maybe that happens, that kind of interaction with the program and, if need be, then, back to the doctor and to the program, every prescription, period.

DR. GROSS: How do you suggest this be done again?

MS. SHAPIRO: Computer.

DR. GROSS: Dr. Epps.

DR. EPPS: In regards to the stickers and I guess the scenario that was introduced, the sticker has your name and your DEA number on it. It is not something that a staff or a nurse or

someone else can substitute.

Also, in regards to birth control, birth control pills and hormonal contraception is contraindicated in certain populations. There are some people who should not take oral contraceptives or Depo or whatever, I mean there is now I guess a monthly injection. There are complications. There is a whole list of not only contraindications, but potential side effects, and everyone should not take them.

Of course, some of my patients come, they have talked about it with the pediatrician, they come with the blood tests in hand, they come with I have already been to my doctor, I am on my birth control pills. A lot of patients are really, really prepared, and I don't think a lot of patients or their parents, if they are a minor, are that ignorant about it.

I mean these people read, they go on line, they talk to their friends. The visit before, I usually give them some literature to look at regarding the side effects and the risks and the

benefits.

So, I agree education is important, I think that it should be ongoing at every entry point possible. If they are seeing me, they are seeing the pediatrician, everybody is reinforcing this stuff, and sometimes the information can change, too, just as before, as someone alluded to, that they used to recommend on the third day of the period, then, it was the fifth day, and changes in the protocols, but I don't think people are just winging it.

DR. GROSS: The last couple of comments have been on the stickers, which is really Question No. 2, so we could move to Question 2. Any other comments on what aspects of the program made the stickers not meet the role they were intended to meet? Dr. Raimer.

DR. RAIMER: Before we go to stickers, I just wanted to comment again. I do think that every patient should have to sign up to be part of the patient registry, and I think that should be done in the physician's office before the patient

is ever given Accutane, that they should sign up, register for the survey before they are ever given Accutane, that that should be part of what has to be done to get the Accutane.

I think it ought to be looked at, an on-line sort of process--might should be looked at, I don't know all the ins and outs about doing that--but at least you could get to the patient a little more quickly with the survey, and I think there should just be one vendor. It is much too confusing having more than one vendor.

DR. GROSS: Thank you. That comment actually is very relevant to Question No 4, which talks about registers, so that is important to note.

Dr. Katz.

DR. KATZ: Part of Question 1 says discuss measurement factors that have contributed to a lack of having accurate numbers, and we keep talking about the response rate of 28 percent to the survey, and that is easily taken care of with mandatory--as other people have alluded

to--mandatory enrollment, and it is not that burdensome.

You are having people sign the consent for two consent forms before they leave the office, before they get Accutane, having bloodwork done or having it done at the lab, and this enrollment form is very simple.

Instead of what we have been doing now, we strongly urge you to fill that, because there could be more restrictions if you don't, instead of that, you also have to fill that out, and you send it from the office, postage paid, and you send it from the office, and if they don't respond to the questionnaire, you get feedback in a couple weeks that they didn't do that, and case closed. It is not even added burden.

So, a mandatory enrollment would eliminate our whole discussion of do we have accurate numbers, what can be done at follow-up, and we can take that 28 percent and push it close to 100 percent very easily.

DR. GROSS: So, really Questions 1, 2, and

4 are all kind of interconnected, which is fine.

Dr. Vega.

DR. VEGA: This is a comment regarding why are we going back and forth on these questions, and why is to assess the pregnancy, stickers, testing, all that. If we think about it in the normal way when the drug is coming to the market, if we had isotretinoin coming down the pipeline as a new drug, and knowing what we know right now, I am sure that we will have no hesitation, no fear, in fact, we will not dare to let this drug go into the marketplace without the shackles of a good, strong mandatory pregnancy prevention program, risk management program, that will help us to control the use and prevent or minimize the pregnancy exposure.

However, we are going backwards, it is already out, and there is a lot of use, and now we are trying to contain, and that is why it is so hard to go backwards, but we need to maintain the forward perspective and try to apply it in a backwards way.

This sounds kind of confusing, but the principles are the same, and we should apply them even when we are trying to read backwards into this issue.

DR. GROSS: Dr. Gardner.

DR. GARDNER: With respect to stickers, I think that we simply cannot examine--I mean we can't recommend any program going forward that does not take into account the opportunity to gather or to communicate through computerized order entry, PDA entry, that is going to be the way that prescriptions are delivered, communicated, and it already is in many places.

It certainly is in institutions, many institutions that have dermatology clinics. We are going to have to address that. Yellow stickers do not address that, so whatever system we have, whether it incorporates yellow stickers for hand-carrying to reach all pharmacies or not, it also has to address these other things.

I would also like to have us look over the next hour or so about what are we going to do about

mail order sales.

DR. GROSS: On the sticker issue, I think the question has been answered as to why there is a disconnect between the stickers and inadequate birth control measures, because that may be impossible to ever assure.

But how about the issue of the inconsistent link between monthly pregnancy testing and the stickers? Why do you think that failed?

Yes, Sarah.

DR. SELLERS: I would like to, first of all, agree with the comments that Dr. Ringel made earlier concerning the amount of information that is intended to be conveyed by the yellow sticker, and again why problems with the sticker may have contributed to the findings.

I would like to go back to my comment yesterday on what exactly the qualification date, what information that conveys, because again, in the S.M.A.R.T. package, briefing package, it states that the date is actually the date a sample is taken, not the date that there is a confirmed

negative pregnancy test.

That seems to be in conflict with the labeling of the drug, which requires two negative pregnancy tests prior to prescribing of the drug.

DR. GROSS: Dr. Kibbe.

DR. KIBBE: I think we are all trying to get our handle around the entire program, and while we address each question, we end up addressing all the questions and all the issues, and there are some human behavior issues, and then there is lack of data issues.

Then, there is an issue that I think some of us are struggling with, and that is how draconian does the risk allow us to become in terms of preventing the risk. I know Dr. Venitz said that he didn't trust the abstinence, it wasn't one of those really great dependable methods.

There is, of course, the medieval admonition that when you are going to be an abstainer, you should get to a nunnery. The real issue is how draconian are we going to be, how forceful can we be in our society, and upon whom

should we exercise the additional level of control in terms of behavior.

I think that if we took a quick run-through, we would all agree that a mandatory survey gets us a lot more information, a lot more data. Whether or not a mandatory survey gets us any improvement in pregnancy rates is completely disconnected from me in my mind. I can't see how mandatorily surveying people gets them to change their behavior.

I also understand that education is a variable and active education versus passive education makes a difference, but 100 percent recall of educated material is absolutely impossible.

I have done it at universities for many decades, and you can't get students who are trying to even get into medical school to remember all the stuff they learned in any one lecture of physiology, and we are dealing with a cross-section of American people.

We just can't expect education to be all

the answer. I have a tremendous faith in the dermatologists. I think they are truly devoted to getting the right result, and they see the results all the time, and it is right in front of them. They are really motivated.

I don't think we need to worry about the physicians wanting the outcomes. I think we have to empower them to get those outcomes. If we have a mandatory survey system and a mandatory registration for our patients and our pharmacists and our physicians, we will have a way of collecting data, and we will still have pregnancies.

The answer really is can we differentiate between the 99 percent or more of women who, when given the option and explained the situation, will be very careful and not get pregnant, from the 1 percent or less of women who no matter what we do on an educational basis, will find a way to have a failure rate, and that is what we are looking at.

If we can get data from the 99 and compare it to the 1, and find some trends or some ways to

get our physicians well informed about what are risk factors, then, are we willing to ask them that, since you are in a high risk and we are not willing to take the chance with you, that you will have to be on one or more forms of birth control that we control as a clinician rather than that they control as a patient, and how draconian do you want to be.

You could very well look at them and say all right, we will start you on this therapy two months from now, but today you are going to the gynecologist and you are going to get an IUD, and we are going to do pregnancy tests, and two months later we are going to start you on this therapy, and two months after the therapy is over, then, we will let you go back to the gynecologist and take the IUD out or something comparable to that.

Now, that is as close as you can get to putting them into 100 percent assuredness, but I am not prepared to say we do that to all of our patients. I am saying let's find a way to figure out which patients are at high risk and offer

them--and I don't know whether that is the exact method--but there has to be something more than what we are getting to.

So, sure, we can recommend to the FDA to go ahead and accept a mandatory survey system and a mandatory education system, and what have you, but it is not going to end pregnancies for women of childbearing age on this drug unless we have with it a more draconian second step.

DR. GROSS: I guess another question is it won't end it, but will it decrease it, and also dermatologists aren't the only one that prescribe the medication as we have heard.

Dr. Whitmore.

DR. WHITMORE: I am not quite sure what question we are on, but as far as--

DR. GROSS: All of them.

DR. WHITMORE: Okay. As far as the survey and registration, I think mandatory survey and registration is essential. I wonder if there is a way we can also have a simultaneous anonymous survey be sent in just so we can be comparing our

data that we are receiving. So, that is one question.

The next is about the yellow stickers and pregnancy tests going to the pharmacy, and things like that. I think we have to remember that the pregnancy test is only going to be helpful in preventing persons who are starting Accutane from starting Accutane while pregnant.

The follow-up pregnancy test is going to tell us to stop the drug earlier than we would otherwise, but we will still be needing to tell the patient that their baby may have a retinoid embryopathy.

So, think remembering that, that our pregnancy test is only going to be effective in preventing persons who are pregnant from starting Accutane, and is going to do nothing else, nothing for the other individuals who become pregnant during Accutane therapy.

DR. GROSS: Sarah Sellers?

DR. SELLERS: No.

DR. GROSS: Dr. Epps.

DR. EPPS: Just a couple of comments. Medicaid requires that prescriptions be written, so if we are of opinion that Accutane should have written prescriptions, then, that could be, too. It doesn't have to be electronic, it doesn't have to be by PDA, it probably shouldn't be. Occasionally, Medicaid, pharmacies may accept a written faxed prescription, but regardless it has to be written, and that would eliminate the hackers and the other people who want to get it to sell it or do whatever they want to do it.

Survey is a good idea if that were to be implemented. As far as registration and pregnancy testing and faxing it to a pharmacy, I don't agree with that. I think there are real privacy issues especially when you are talking about minors.

It is not like a WBC count, you know, it is not like a white count. If you have one pharmacy and you are in a small town, and if there are certain pharmacies that do it, I mean there are real confidentiality issues there.

That's enough.

DR. KWEDER: Excuse me for interrupting the order, but I am hearing a lot around the room, there is a back and forth about surveys and registries, and I am not sure that we are all talking about the same thing.

I wonder if it would be helpful perhaps after the next break if the staff could present a description of the S.T.E.P.S. program which employs both, and they are very different. You know, the registration and the survey itself are different, and they have raised for us and the company different kinds of issues with regards to privacy and what is acceptable to OHRP.

We have some slides that might help clarify some of that, to try and put a framework around that before final decision and recommendations are made.

DR. GROSS: Do you want to pull those together, because we may get to them before lunch?

MR. LEVIN: Could we also have a description of the other program?

DR. KWEDER: That is what I mean.

MR. LEVIN: I mean both programs.

DR. KWEDER: What both programs?

MR. LEVIN: Clozapine and the Thalidomide programs.

DR. KWEDER: I think so. I think we can pull that together.

DR. GROSS: I am going to take the prerogative of the Chair to say it sounds as though we are pretty much done with Question No. 1. There may be some issues that come up later on, and that's fine, but to move us along.

Some of the issues that have come up for the second part of Question 1 regarding measurement, surveys, mandatory surveys, rewriting the survey, so that it is at maybe a seventh or eighth grade level, implementation factors.

We talked about stickers, which is really the next question. Use of FMEA, qualitative assessment, that the survey would have to be rewritten to include many more possible factors.

So, those are some of the issues that were raised. Also, it was pointed that while zero

pregnancies is our goal, no matter what we do, we are probably never going to be able to reach that level.

On Question No. 2, we have had a few comments on stickers. Would anyone like to comment on what aspects of the program made them ineffective? The use of the stickers was high, but apparently it didn't prevent pregnancy.

Dr. Katz.

DR. KATZ: That is not a proven statement. The lack of link between the stickers and whether patients really got pregnancy tests because we were told earlier that when doctors' offices were checked, they did have pregnancy tests on the chart, which was my initial question, because when people are asked on that survey, that onerous survey, whether they had pregnancy tests, they may forget that the pregnancy test was included in the blood tests.

I have had people ask me, oh, was that the pregnancy test, too, and they have to be told that. A lot of times when they get the regular blood

tests, you don't repeat, now, this time I am getting a CBC, hepatic profile, triglycerides, and pregnancy test. You are repeating the blood tests, and reminding them about the pregnancy. They may not have that, they may disconnect that.

So, we are getting this disconnect data from the questionnaires of 28 percent of people that return that, that said no, I got the stickers, but I didn't get the pregnancy test. Well, that is not necessarily true.

DR. GROSS: Anyone else have any comments on the stickers per se? Dr. Bergfeld.

DR. BERGFELD: I would like to say I like the stickers, and I like the stickers because it is an imprint on the physician that when you have to move to using the stickers, you have to be constantly reminded of your responsibilities. So, it is a reminder to the physician.

I would also like to comment that I would like to see addressed on the next folding out of whether it be a registry, a registry and survey, that you look very carefully at what you really

want to glean from that, and I will definitely say has to be simplified and easy to read.

Included in that, the physicians need some kind of flowchart that they can attach to their medical record, whether it be paper or computer, so that they can have a flowsheet that these records just don't go in a patch-like way into the patient's record. It would be very helpful to have a drug list record.

Thank you.

DR. GROSS: Dr. Raimer, did you have a comment on stickers?

DR. RAIMER: I did. I just wanted to reiterate something that was brought up yesterday. I think we should continue to re-educate the physicians also. It has been almost two years since most of us signed up for the S.M.A.R.T. program. I think you should have to re-enroll every year.

I think it should be an on-line program where you actually take a little test and you have to say, yes, I realize the second pregnancy test

has to be done during the menstrual cycle.

I think the doctor should have to get all the answers correct before they get the stickers. They can take the test as many times as they need to, but, you know, just a short exam to be sure they know all the facts and be re-educated every year, and then they should get a sticker that is good for a year, have to redo it every year.

DR. GROSS: So, this is a different kind of sticker. This is a sticker for the physician, not the patient.

DR. RAIMER: No, it is the yellow sticker. You get a supply of yellow sticks from the company. So, you get your resupply of yellow stickers each year after you have passed the test, just to be sure you remember all the things you are supposed to do, but a flowsheet would not do the same thing.

DR. GROSS: That is a new suggestion. Would anyone else like to comment on that? Basically, annual recertification of people who are using Accutane or related drugs, should that be part of a program that we are going to recommend?

DR. WHITMORE: I second that idea and would say that the stickers can just expire one year from the time they are sent out.

DR. GROSS: Yes.

DR. WILKERSON: A couple of comments at the risk of drawing ire from the pharmacy lobby. I mean the role of the physician is to diagnose and to prescribe. The role of the pharmacist is to fill the prescription according to proper labeling. The pharmacist is not a clinician.

I would really hate to draw pharmacists into this any more than they have. Their job is not to do the doctor's job, to be sure that the patient has had their pregnancy test.

That lands squarely on the shoulders of physicians to be sure that patients are following the guidelines. It is not the friendly pharmacist down the street who should be entering into the exam room to make sure that the patient is doing what they should be doing, and the doctors should be doing.

I do like the stickers. I think it is

like a badge. It indicates to the patient that I have taken some additional study, I know what I am prescribing here, and I am the one who can prescribe this for you.

I like Dr. Bergfeld's idea about having some type of flowsheets that prompt physicians and nurses to order the right test and to be sure that the things are done in a timely fashion.

These stickers or special prescription pads, however we want to look at this, I think is the other thing. We could look at a triplicate form, such as used in many states for narcotics, is yet another way to track physicians and to track enrollment of patients in the data bank.

DR. CRAWFORD: Dr. Wilkerson, yes, you are about to draw some ire. I just must respond as an associate professor in the college of pharmacy and as a pharmacist.

I agree that the pharmacist's role is not to diagnose. I disagree that the pharmacist is not a clinician; if anything, I think the role of the pharmacist should be increased in the risk

management program because it has been brought up--I didn't particularly agree with the comment yesterday that the pharmacist should be a policeman, but the pharmacist is the last step typically in the drug use process before it gets to the patient, and the dispensing process is much more than simply filling the prescription.

It also involves or should involve patient education in case there are comprehension problems, patient counseling in case there is a need for customization. It was not determined at the prescriber-patient relationship where the pharmacist may get back in touch with that prescriber, but I disagree with the fact that it is just a technical process.

DR. GROSS: Any other comments on Dr. Raimer's suggestion of annual physician recertification by I guess some simple, straightforward tests?

Dr. Bigby.

DR. BIGBY: I think it's a good idea.

DR. GROSS: Brevity is the soul of wisdom.

Any other comments? Ruth.

DR. DAY: There would be a way to combine the sticker with the flowchart idea and also meet some other concerns about what does a sticker mean in terms of the qualification date.

Each sticker could be at the top of an 8 1/2 by 11 piece of paper, and to peel it off to put on somewhere, there is a checklist, so the physician would check through each thing that has to be met because at present, if you have looked at that sticker recently, it just says that you are prescribing this based on whatever is in the contraindications and warnings of the package insert.

So, if there was a checklist that the physician checked off and then took off the sticker and put it on the prescription, that would be very good, and that checklist could then be dated and put in the patient's file at that time.

So, this is in the interest of decreasing the paperwork load and the pieces of paper floating around. It could all be together, and that would

be documentation of what happened on that day.

DR. GROSS: Other comments on Dr. Raimer's suggestion? Mr. Levin.

MR. LEVIN: I just want to make a suggestion that we are talking a lot about changes, and yet we have two programs to draw on that are managing risk, we think, better than this effort has.

So, I would like to suggest that rather than spending a lot of time with each of us coming up with our little or not so little, major ideas, and I have lots of them about what could improve this program, that we really learn from the experience with the S.T.E.P.S. program and the clozapine program, and then come back together and say do those solutions begin, using those programs, those approaches begin to offer us an opportunity to build on experience where, by the way, there is data, because whatever we are proposing here, we are not going to know its effectiveness for another couple of years.

I would be remiss as a consumer advocate

not to express my annoyance, to put it mildly, at the fact that we are here discussing the lack of data because after the Advisory Committee in the year 2000, and I was part of that process, asked for a lot of what we are talking about asking for today, and which, in fact, Roche today is coming forward and saying we are willing to do.

If that had been done when the Advisory Committee had asked it to be done, we would have much better data to have this discussion with. So, I just want to caution that all of these things we are suggesting which are new will need time to get evidence that they are successful or not, and in that interim, more people are going to be hurt because we haven't taken an action.

We have a responsibility to prevent further injury if we can prevent it, and it seems to me that we have an opportunity to learn from two programs, which as far as I know have been apparently more successful in controlling risk and still permitting appropriate access.

So, I would suggest that we have lunch and

then listen to a description and explanation of those programs' successes and failure, and then come back and draw on that experience where we actually have data that backs up various parts of those programs' successes and failures, and then have a discussion.

DR. GROSS: Mr. Levin is hungry, so why don't we recess because we don't want to have an unhappy committee member. We can all sate our appetites and we will see you--do you want an hour for lunch--let's get together at 12:30.

[Whereupon, at 11:45 a.m., the proceedings were recessed, to be resumed at 12:30 p.m.

A F T E R N O O N P R O C E E D I N G S

[12:35 p.m.]

DR. GROSS: Dr. Uhl will make the presentation on risk management programs that Dr. Kweder mentioned earlier.

Dr. Uhl.

FDA Presentation

DR. UHL: We have been asked to try and address the program that is used to monitor and to dispense Thalidomide. Up here with me is Carl Kraus. Carl is a medical officer from the Division of Special Pathogens and Immunologic Drug Products. Carl is the medical officer in CDER for Thalidomide.

I am going to go through a couple of slides and then Carl is going to go through more of the intricacies of the program for Thalidomide. Dr. Trontell will address clozapine.

[Slide.]

The program for Thalidomide is called S.T.E.P.S. It is the System for Thalidomide Education and Prescribing Safety. The company that

manufactures and distributes Thalidomide is the Celgene Corporation. I am not sure if there is anyone in the audience from Celgene, but if they are, it will obviously be the Chair's prerogative if he would like them to address any questions, as well.

[Slide.]

In your briefing package, there was information provided about the S.T.E.P.S. program. This is just to reiterate what are the program objectives for S.T.E.P.S.

The objectives include to prevent fetal exposures to Thalidomide, to educate regarding the risks of Thalidomide, to provide procedures to reduce the risk of fetal exposure to Thalidomide, to identify at-risk behaviors by surveying patients and prescribers, and to provide a mechanism for intervention and remediation when at-risk behaviors are identified in S.T.E.P.S.

The S.T.E.P.S. program is also a mechanism for restricted distribution.

[Slide.]

I am going to walk through the original S.T.E.P.S. program very briefly. There is now a new program that has been implemented.

The original S.T.E.P.S. program, very briefly, the patient had the physician visit, the consent is signed. This is a consent by the patient to participate in the S.T.E.P.S. program. A prescription is provided, and a pharmacist, who is registered within the program, is able to dispense the product.

A survey is provided to the patient with the dispensing of the medication. The drug is dispensed to the patient. This survey subsequently is completed by the patient and is given to the Boston University Slone Epidemiology Center. They review this survey and take action as to some of the responses that the patient has provided.

[Slide.]

Very briefly, there were some problems identified with the old S.T.E.P.S. program, and there were areas of improvement that were specifically targeted. For example, the Boston

University survey identified at-risk behaviors basically after the drug was dispensed.

There was a time delay to identify these at-risk behaviors and to intervene, which was felt to be suboptimal, and the Boston University Slone Epidemiology Center's survey, the primary focus was not for real-time patient intervention.

There were other areas of improvement, such that the program's design could do more to assure the compliance with the program procedures, and the example of this is the pregnancy tests that are required with the S.T.E.P.S. program.

I erroneously spoke yesterday that the patients have two pregnancy tests prior. They actually have one pregnancy test within 24 hours--that pregnancy test must be done within 24 hours of the patient getting a prescription for Thalidomide. Then, the patients have weekly pregnancy tests for the first month, and then monthly thereafter.

The frequency of testing is a little bit different if you are a woman who does not have

regular menses.

The original S.T.E.P.S. program, there were limited risk group classification, basically just based upon male or female. It did not include strategies that targeted this. This is adult females of childbearing potential who would obviously be at a different risk for pregnancy to adult females not of childbearing potential.

There were other things that were identified such that the program didn't utilize current technologies to target specific risk groups and interventions for specific risk groups. There were issues with current technologies about record availability, storage, management, archiving, et cetera, and then also the efficiency, quality of accounting, auditing, reporting of the S.T.E.P.S. activities.

[Slide.]

So, a new S.T.E.P.S. program was launched July 30th of 2001. These were basically modifications to the original S.T.E.P.S. program. Many of the elements were the same. These are some

of the similar elements.

There is registration of all prescribers, all pharmacists, and all patients within the S.T.E.P.S. program, that is, anyone who is involved in writing for the drug, dispensing the drug, or receiving the drug are registered within the program.

There are educational materials, which includes brochures and videotapes. There are materials for all three elements - prescribers, pharmacists, and patients. There is the issue of patient counseling and education. There is a limited supply, such that patients get a 28-day supply, and the Thalomid comes in a blister pack. It is a unit of use packaging.

There is also a mechanism for follow-up of suspected fetal exposures whether the patient be male or female with a toll-free number for notifying Celgene.

It is interesting to bring this up in that there is not a distinction between pregnancy or positive pregnancy test, and what Celgene focuses

on in the Thalidomide S.T.E.P.S. program is a positive pregnancy test, hence, getting around your issue of what is the definition of pregnancy when you are near the Potomac River. The flag for the S.T.E.P.S. program is a positive pregnancy test.

Other of the same elements is that there is no blood donation, and the issues of contraception for females of childbearing potential, and the use of condoms for males who are taking the drug.

The frequency and periodicity of pregnancy testing was not changed with the implementation of the new S.T.E.P.S. program.

[Slide.]

What the new S.T.E.P.S. program did was to have more classification along patient risk stratification. Adult females of childbearing potential, adult females not of childbearing potential, female children of childbearing potential, female children not of childbearing potential, adult males, and male children.

If you remember from my slide yesterday

about the demographics of Thalidomide users, the age distribution was from 1 to 100.

The new S.T.E.P.S. program has consent forms that are computer generated, and they are generated specific to the risk category for the patient who is to receive Thalidomide.

There are specific information that get entered, such as the patient's date of birth, the address, and the diagnosis for which the drug is being used to treat.

What is mandatory is that the patient and the physician and the pharmacist must participate in the registry, and they must use this telephone interactive voice response system, which Celgene, the company, administers and performs interventions based on this IVR. I have a subsequent slide to talk about the IVR.

There is then a patient follow-up survey, which is performed by the Boston University Slone Epidemiology Center. This survey is not mandatory, it is optional, and Dr. Mitchell can certainly address this a little bit more, the issues that

they have had with doing the survey and some of the targets to get to quality assurance and program evaluation.

But the distinction here is that the registry has mandatory elements for all patients, providers, and pharmacists, but the survey is optional, is not mandatory.

[Slide.]

The IVR is a technology that uses interactive voice response system. It uses an automated telephone-based survey. This is administered by the company Celgene. The survey questions are tailored to the patient's specific risk group.

The patient calls in, as well as the pharmacist and the physician. They call in to this number. They have an identifier that they enter for the patient. It is a unique identifier that is based on their Social Security number.

According to what the patient keys in, in this IVR, it asks specific questions to get at at-risk behavior, and if there is patient at-risk

behavior identified, it triggers real-time interventions to Celgene, whereby the patient is transferred to an actual person who will talk to them about their at-risk behavior.

The IVR system is also used by physicians or the physician administrator to enter the results of the patient's pregnancy test. The IVR system is also used by the pharmacist to get the information that that prescription has been activated and get a dispensing number.

Dr. Kraus will walk you through some of the elements of this complicated--

DR. KRAUS: It is not as complicated as it may seem, I think.

[Slide.]

Initially, what occurs with the S.T.E.P.S. program at the initial physician visit is the informed consent process occurs after discussion of the risks and benefits of Thalidomide therapy, and the consent is signed.

Of note, after this visit, the physician is required to call into the IVR system and answer

a number of questions that are related to the physician side of the IVR system.

The prescription is provided only after the patient has a negative pregnancy test within 24 hours, as well as having instituted some type of highly effective therapy for contraception at least three days prior to the prescription being written.

So, the consent is signed, and that is called in to the IV, the physician calls in to the IVR, and when I say that, after the consent is signed, the patient also calls in to the IVR. I think I wrote that on the second little arrow there.

Then, once the two parties, the physician and the patient, have called in to the IVR system, a number is generated that the physician writes on the prescription, which quote, unquote, "activates" the prescription, so that when the script is taken to the pharmacy, the pharmacy recognizes that this indeed is an activated script, will call in to verify that with the IVR, and then Thalomid is given for a 28-day supply.

Now, at the initial institution of the system for the patient, there is weekly pregnancy testing for the first month. Assuming they are all negative, then, it goes to monthly thereafter.

Any time during the compliance evaluation--and I consider the IVR system to really be a compliance issue as opposed to the quality assurance of the survey which would follow--there can be flagged IVRs, in other words, the most common reason for flagging is an outdated pregnancy test.

So, basically, if the pharmacist plugs into the IVR the date of the pregnancy test and it doesn't comply with the seven-day requirement prior to giving the prescription, then, a flag will go up. The pharmacist will be put in touch with a Celgene telephonic representative, and the script can be re-evaluated.

Either the patient has to go get another pregnancy test or they call the physician and see if there is a more recent one. Typically, that patient will not be given Thalidomide until an

adequate pregnancy test has been performed.

I put two things in yellow here, Celgene mails initial survey with unique identifier. That has not yet been implemented, and a blinded patient was sent to Slone has not been implemented yet.

Basically, what is going to be occurring, the identified information on the patient will be provided to the Slone Epidemiology Unit to be mailed out for the follow-up survey, and only Celgene will have and maintain the list as a full registry, but Slone will not as far as who these patients are to be more in accordance with HIPAA compliance, and so forth.

That is sort of the gist of this new S.T.E.P.S. program. I am more than happy to entertain any questions you may have on that.

DR. GROSS: Are there any questions? Yes.

DR. BERGFELD: I have a question of you if you don't mind. Could you tell me the numbers of patients involved in this study?

DR. KRAUS: Sure.

DR. BERGFELD: And the distribution of

age, particularly the reproductive female.

DR. KRAUS: I was expecting that question.

[Slide.]

Approximately 65,000 patients--that is incorrect--it is actually 80,000 now, so the number is outdated, since July 2001. Just looking at the third quarter information from last year, there were about 50,000 surveys completed, and when I said that there can be flagging from the IVR, about 5 percent were flagged, and the majority, over 90 percent were related to outdated pregnancy tests. Some were related to other pharmacy issues, and some related to other IVR issues.

DR. GROSS: Why did you make the survey optional in the new S.T.E.P.S. program?

DR. KRAUS: You mean going from mandatory to optional. Much of it has to do with the fact that in order to have all the appearances of being a quality program for the FDA to ensure the safe and effective use of the drug, and not to infringe on the possibility of being misconstrued as research, it was decided to make this into an

optional survey since the compliance portion of the IVR is mandatory.

So, there really are two aspects of this. One is the mandatory IVR portion, which all patients, pharmacists, and physicians are required to participate in, then, there is the optional follow-up survey, which is a quality issue for the program.

I think we had about 40 to 46 compliance with the survey as far as follow-up goes. Not everyone sent in the--

DR. KWEDER: It is a little confusing because even on the slide, it is often call the IVR survey, so it's like there is two surveys, but the one that is associated with the IVR component is not optional.

It is the follow-up survey that is optional, and the reason that it is optional is because--it used to be mandatory or was stated to be mandatory--and OHRP raised significant concerns about it because they felt that despite our imploring that this was really a quality assurance

tool, they felt it was more of a research tool, and if there was any intention to collect the information and publish it in some way, so that it might be useful for another program, that constituted research, and therefore could not be mandatory.

DR. GROSS: Dr. Cohen.

DR. COHEN: I would be interested in knowing, well, first of all, how many patients are on the S.T.E.P.S. program right now, are involved with the S.T.E.P.S. program, and then, second, what is your general assessment as far as acceptability to patients, physicians, and pharmacists, what kind of feedback are you getting from them?

DR. KRAUS: It should be very much recognized that the patients that are enrolled in S.T.E.P.S. are probably very, very different than those that would be enrolled in Accutane risk management program.

These patients typically take Thalomid for four months of therapy. The majority of them are oncologic in nature, and 90 percent or more are

taking this for some oncologic diagnosis whether it be multiple myeloma, renal cell carcinoma, what have you, and there is a significant amount of interplay in a hospital setting, as well as an intense oncologic clinic for interaction with the S.T.E.P.S. program.

Now, when the physician enrolls in the S.T.E.P.S. program initially, there is a designee on the enrollment form that states who will be the S.T.E.P.S. coordinator for that physician, whether it be the physician himself, someone in the office to assure compliance with the safety requirements of Thalomid prescriptions.

DR. GROSS: Dr. Day.

DR. DAY: In those cases where there was a flag and an intervention was then required in order to continue, how long was the interruption of treatment, and is there a window that is allowable, and then can someone here comment on interruption of treatment with Accutane and similar products, what consequences that might have for the patient?

DR. KRAUS: If a flag occurred between

8:00 a.m. and 8:00 p.m., the hours of the manned telephonic survey, there will be direct intervention right then and there, and hopefully, the problem can get resolved quickly.

If it occurs after 8:00 p.m., then the script will no longer be valid until the following day when intervention can occur.

DR. DAY: But the intervention might then require additional action, such as an additional pregnancy test, it was out of date by a day or something like that. Do you have evidence about interruption of treatment?

DR. KRAUS: I have no data on interruption of treatment.

DR. GROSS: Robyn Shapiro.

MS. SHAPIRO: How is this paid for?

DR. KRAUS: How is this paid for? Celgene. It is all company sponsored, yes.

DR. GROSS: Dr. Schmidt.

DR. SCHMIDT: This stuff is used for a lot of skin diseases, too, for ENL, erythema nodosum leprosum, prurigo nodularis, and lupus, and it is

actually quite effective, so we use it in patients who are not, you know, cancer patients, and it's about $600 a month.

So, what I would like to know is how much of that is the medication, and how much of this is the program, and then the other thing is I have had some older women on this thing, that one of them called me one time and she said everybody else is having all the fun, and I said what do you mean, and she said, well, I got this survey that called up and asked how many times I was having sex every day.

So, some of these things, to me, she thought it was real funny. I told her when they called back again, to tell them with the football team.

DR. GROSS: Actually, I have used the S.T.E.P.S. program myself on one occasion for a patient, and did not find it onerous. It was also interesting. The patient had a survey that I did not observe. The patient filled it out, put it in a sealed envelope. I never knew what the patient

said, so I thought that was good.

Any other comments? Jackie.

DR. GARDNER: Perhaps we heard yesterday, did you tell us how many pregnancies have occurred on the S.T.E.P.S. program among the 80,000 people?

DR. KRAUS: There was one, and I know Dr. Uhl, I think had a slide on that yesterday.

DR. KWEDER: There have actually been a number of false positive tests on the program, and the database is rich enough that you can actually go in and determine that those were false positives.

DR. GROSS: Mr. Levin, back from a full lunch.

MR. LEVIN: Again, my appreciation to the Chair.

I guess the question would be of FDA, is it FDA legal counsel opinion that a mandatory survey is going to be thought of as research, because we have been talking about mandating a survey, but if FDA is telling us that it is FDA counsel's opinion that that is inappropriate

because it becomes research rather than quality improvement, we should know that before we make a recommendation, for example, that there be a mandated survey if that is simply not going to happen.

DR. KWEDER: I am not FDA counsel, I would never pretend to be, but I think the general answer to that question is if there is a survey, it needs to be clear what the purpose of the survey is, and that has to be directly related to safe use of the drug.

For example, the IVR survey is clearly that. The follow-up survey, which looks more at some of the qualitative aspects of the program and how information is communicated or not communicated, really doesn't meet that standard as clearly, despite the fact that we continue to believe it is highly desirable in order to continue to improve the program, and take away burdens that may not be necessary.

So, that is not a direct answer to your question, but we will work to ensure that the

elements that are mandatory are things that will be of use to the safe use of the drug.

DR. GROSS: Dr. Whitmore.

DR. WHITMORE: I was just going to answer Dr. Day's question about discontinuance for a short period of time off Accutane. It makes no difference. We dose based on a--for most of us I think--dose based on a cumulative amount of drug getting in over whatever period of time it is, so for them to be off of it for a week is not going to do anything.

DR. GROSS: Dr. Bergfeld.

DR. BERGFELD: I didn't hear the answer to the denominator in the study of 80,000 individuals who have participated actually in the program, and you had one pregnancy, but how many were women in childbearing age who could possibly get pregnant?

DR. UHL: Actually, we did present that yesterday.

DR. BERGFELD: Would you repeat it?

DR. UHL: Yes, ma'am. The females of childbearing potential are 5 percent of the

patients. It is approximately 4,000, and that has been over the six years that the S.T.E.P.S. program has been in practice.

DR. GROSS: Thank you.

Now, I believe the FDA has some information has some information they want to present on the Clozaril program.

DR. TRONTELL: The information that we have on the clozapine program, I will invite Chad Clark, if he is in the audience, to talk about the specifics of how individuals are registered, which is to clarify the distinction between a registry and a survey.

In the case of clozapine, individuals are tracked by their Social Security number. There is a registry solely for those individuals who are not to be rechallenged with the drug based on their prior experience of a lowered white count with that.

There is no survey because, in fact, some component of patient behavior really doesn't apply in the case of your white count. So, the

distinction that we wanted to make clear in the discussions earlier, in which Dr. Kweder I think has already articulated very well, registering a patient for purposes of tracking, to know your denominator is perhaps one process.

Collecting ongoing information pertinent to the safe and effective use of the product, much as is done through this IVR module with Thalidomide, is yet another component of safety and effective use, that is considered allowable and able to be made mandatory as a condition of safe use of the drug.

But when you talk about important information that is pertinent about risk factors, failure, mode and effects analysis that are collected through the voluntary patient survey, that is construed by the Office for Human Research Protection, known as OHRP, is not something that we can mandate for patients.

But if you want more particulars, I apologize, we have some individuals with pharmacy practice that can talk about their individual

experience of how you get registered. Let me also make one clarification to my remarks yesterday.

It is pharmacies that are registered, not individual pharmacists for the program.

Let me give one additional piece of information that may or may not be pertinent to some of this discussion. All of these programs have less than 100 percent compliance documented with them in terms of what happens at the pharmacy.

Occasionally, a product may be released without the pharmacist having had the opportunity to do the full check. That has occurred with Thalidomide, it has occurred with clozapine, and we had evidence to suggest that has happened with Accutane, as well.

The system, as you have seen in the case of Thalidomide, to date has one pregnancy exposure among 4,000 women over a relatively extensive period of time of its use.

DR. GROSS: Any questions or comments on clozapine?

Hearing none, I would like to ask Roche if

they would briefly present four or five slides showing the proposed program. Dr. Huber will present.

Hoffmann- La Roche Presentation

DR. HUBER: Thank you.

I would like to point out that in the design of this system, we did incorporate the elements of the S.T.E.P.S. program, as well as the clozapine, and as we walk through, I will try to point out how they are linked in.

[Slide.]

First of all, I would like to point out that this path across the top here, this registry is analogous to the IVR registry of the S.T.E.P.S. program. It is a single data place where the interactions occur.

We have not specifically decided on IVR. We are interested in hearing your input on that, because it is not clear that a telephone is the best interaction. We assume an IVR is probably the basis, but there may be web-based and other modalities available, but at this point in time, I

would say work under the assumption we are basically talking about an IVR type system.

The initial visit is analogous to the S.T.E.P.S. program in that there is a determination of childbearing. There is a screening pregnancy test, and this is literally a first pregnancy test to make sure the patient is not pregnant before they even start. There is no point in getting them going down the pathway if we already know they are pregnant.

Education, informed consent. This is basically what we do now in the S.M.A.R.T. program, and the same thing is also occurring in the S.T.E.P.S. program.

The patient then gets entered. This is a registered physician, and this gets entered into the registry.

[Slide.]

You will get a patient ID back. We were intending that the system would generate a patient ID number to avoid privacy issues such as use of Social Security numbers.

[Slide.]

Once the physician receives that ID number, this interaction with the system is what they are describing in the S.T.E.P.S. program as this IVR survey that the patient does.

We have not designed the detailed questions that go here yet, the methodology used. The intent is that these questions would measure some form of compliance with the program. In other words, they would be questions about did the patient understand, are they on contraceptives, are they using them appropriately, et cetera.

There is a lot that has been developed over the past five years, and how you can do this maybe a little better. Randomness of the questions, so patients don't memorize patterns, variation on scripts.

The intent would be that this data would be asked the patient, they would answer. Their responses are captured in the registry, so in parallel, this is doing two things. There is an intervention here in which you are potentially

identifying an at-risk patient, but at the same time you are building the data set that you can use for assessing overall what patients are the highest risk, for example.

This occurs once again into the same registry, very analogous to S.T.E.P.S.

[Slide.]

The patient then goes and sees the physician. At this point, they do a laboratory-confirmed pregnancy test. This is the same concept as clozapine. In S.T.E.P.S., the physician basically does an attestation that there is a negative pregnancy test and enters I believe the date.

We are asking actually that the pregnancy test result go into the system. As was mentioned yesterday, there are some concerns about how the mechanism of this is done. We don't want to have delays, so it may be an interaction with the system to call and say there is one, and then a follow-up with the fax.

Ideally, you would love to have, if you

have electronic laboratory databases, electronic transfer, there are some fundamental issues with that, but the intent will be, in this registry up here, will be a laboratory-confirmed negative pregnancy test, as well as the script will get dispensed with the qualification sticker is what we propose now and the patient ID.

[Slide.]

So, the registered pharmacy, as analogous to S.T.E.P.S., verifies this, essentially, checks it is authorized, and what the system will tell him when he calls in, is was there a patient ID registered, did the patient get through this test, and was the laboratory test negative.

We are proposing that that be a yes/no question in the system. One of the concerns from a privacy point of view, as was stated several times, it is one thing to walk to a pharmacist with a white blood cell count, we are very concerned with walking into a pharmacist and handing him a pregnancy test.

The other thing is we don't want the

pharmacist necessarily to get the pregnancy result here, because we think it would be somewhat embarrassing if the pharmacist was the first one to inform the patient at the counter that they are pregnant.

We think it would be more appropriate that that result be channeled back to the physician, and if the patient does get to a pharmacist, it is simply no, you need to call your doctor.

We do not have an additional survey intended into this system. Our intent is that the data that needs to be collected regarding compliance with various patterns, with behaviors, et cetera, we believe that should be captured as part of the overall process.

Once again, its intent is dual. It is an intervention, but then we can also collect data for assessment.

Thank you.

DR. GROSS: Thank you, Dr. Huber.

What you just described is summarized on your presentation from yesterday, for the

committee, on page 82 and 85, if anyone wants to look at that.

Questions? Dr. Bergfeld.

DR. BERGFELD: Thank you.

This presentation of the possible registry and the initial visit through the follow-up, et cetera, this is a combined program of all of the isotretinoin producers?

DR. HUBER: Yes, we would envision a single process.

DR. BERGFELD: And that would include also redoing the patient information, physician information sheets, which would also be a combined, or would you still have separate everything?

DR. HUBER: I think we would have the patient educational materials being combined. There may be some discussion on details of that.

DR. KWEDER: What we would like to hear is what you think about that.

DR. BERGFELD: I think that is what should happen.

DR. KWEDER: What should happen?

DR. BERGFELD: That it should be a combined effort, that it is too confusing to us to have all these different groups with different things that we have to do.

One combined package for the whole drug isotretinoin is the way we would like to go.

DR. GROSS: Any other questions? Dr. Bigby.

DR. BIGBY: Two questions. One thing that I missed, in this system, how is it ascertained when a woman gets pregnant?

DR. HUBER: None of the current risk management programs ascertain when a woman gets pregnant. The only thing we can do is detect pregnancy prior to dispensing of the product for the next treatment.

So, what you do--it's a 30-day cycle, we may end up modifying it to 28, we can discuss that--but at the end of the day, basically, on a monthly average is when the patient will get seen by a physician, have a pregnancy test, and receive one month of treatment.

That is very analogous to Thalidomide for the second treatment on.

DR. BIGBY: The other question I had is in the booklet, on page 55, there is a description about the education in the first 30-day period, and it says, "This includes patient viewing of the isotretinoin video, review of comprehensive written materials, and isotretinoin pregnancy prevention and risk management for women," et cetera.

Where do you envision that people view the video?

DR. HUBER: Generally, that is done in--my understanding is that is offered in the physician's offices. I would defer to the dermatologists how they handle that.

DR. GROSS: Dr. Day.

DR. DAY: Evidently, the percentage of people who view that video is very low. I don't have the accurate data, but I understand it is in single digits percent. So, if you can comment on that, and also if we were to go forward with this program as you have envisioned it, how long would

it take to implement? So, thinking about the patients who would still be continuing under the present plan while the implementation is taking place.

DR. HUBER: Your first question, with regards to the video is low, but now that we are actually spending more time with the behaviorist as opposed to some of the other people we are traditionally talking with, drug safety, that is too surprising we are finding. Videos are actually fairly ineffective. As an educational tool, a lot of people just don't watch videos.

One of the reasons, when we developed this, it was a supplement, it was never intended as the primary tool. So, one of the things we are looking at is we do have multiple modes of teaching. I mean there already is the booklet, there is the other educational materials, and there is the video. Exactly how that will be handled going forward, I do not know.

With regards to implementation, it somewhat depends upon the level of the complexity

of the program that is agreed upon. I would have a hard time giving you--it is not something that gets done overnight, let's put it that way.

DR. DAY: Well, we can appreciate that, but just in the basics of what you have told us, is it on the order of six months, a year, two?

DR. HUBER: You are usually talking 6 to 9 months is our understanding. If you know what your design specifications are, you can get it done in that time frame. The concern is if you start changing details of the design and things, then, it gets substantially longer.

DR. DAY: Well, more fleshing out of the provision of how the patient is going to get the materials would be a helpful component here. Short of at the physician's office, having to go into a separate room to watch a video, I mean just what are the mechanisms? It would need to be specified. I am not asking for right now.

DR. HUBER: We would envision that that would continue as we pretty much do it today. We provide the materials to the physicians, and then

they manage that to the patient for the upfront materials.

DR. GROSS: Dr. Honein.

DR. HONEIN: Yes. Using the unique ID numbers as you have proposed, how would you identify duplicates within your system either because of multiple courses of treatment or prescriptions from different physicians, or even potentially longer term subsequent treatments by women who have previously had an exposed pregnancy during it, which maybe you would want to identify for separate intervention?

DR. HUBER: If I understand the question, it would be how do we identify a patient, for follow-up, we would see them in the system because we assume they would go back to the same physician.

DR. HONEIN: But they might not.

DR. HUBER: If they come back from a different physician, that is an issue. If they would go through multiple physicians, how we would identify that it was the same patient in the system, that gets very difficult unless you start

having true identifiers of the patients in the system.

DR. HONEIN: How about a second course of treatment a year later? You would expect the physician to maintain the link to that ID numbers and be able to locate that a year later?

DR. HUBER: Well, we hadn't actually thought through that, but on the other hand, we didn't see that as an issue, because from our point of view, the important thing was the pregnancy risk management through each course of treatment was the focus of the design.

DR. GROSS: I have a question for you. Have you considered using the six risk groups that are in the S.T.E.P.S. program including adults and children, men, and women?

DR. HUBER: No, at this time not. We will probably focus on females of childbearing potential as a single risk group. One of the advantages of this proposal is given the volume of data we will have, which will be substantially larger than the experience S.T.E.P.S. has, we would hope that we

would be able to identify more quickly patterns that point out specific high risk groups, and then we may need to adapt to that.

MR. LEVIN: Just a point of clarification on the issue of duplication. The registry is not anonymous, am I right, there would be patient information within the registry, it is only the unique number that goes out?

DR. HUBER: Yes.

MR. LEVIN: So, theoretically, if I am correct, you would still have a way of spotting or flagging a duplicate. I mean you have enough information that you would recognize that that is the same patient coming back into the database.

DR. HUBER: The problem is accessing that information, can a physician go in and search and see if that patient already exists, and I just can't answer that question.

MR. LEVIN: Couldn't the registry do that? That is what I am getting at. In other words, the information goes forward to the registry, the registry has other demographic information that

identifies a patient specifically, it seems to me it is taken care of.

The registry can do the search and say whoops, you have been in here before with this number.

DR. HUBER: My technical people are saying yes, we could do that.

DR. GROSS: Brian.

DR. STROM: Two questions. In the system you are proposing, who are you proposing as the enforcer? In other words, who is the primary ultimate body who is responsible for making sure that the patient gets the pregnancy test before the drug gets dispensed?

DR. HUBER: At the end of the day, in this system, if the pregnancy test is--I mean the pharmacist has to go into the system prior to dispensing, so I guess in answer to your question, if the pharmacist doesn't see the system say it's okay to dispense, they won't dispense the product.

So, from that point of view, the final check is the pharmacist to ensure that the registry

has okayed the patient.

DR. STROM: Let me respond to it in two ways, and then I have a second question. One is the fact that you had to pause to think about it. The second, which relates, is in the current system, in the S.M.A.R.T. system, the pharmacy is also the enforcer via the sticker system, and it is not working.

So, I guess my concern is in whatever system--and obviously, there are lots of details to be worked out--I think where the current system has failed is having a clear enforcer who has a vested interest in making sure it happens, and I am concerned about making the pharmacist the enforcer. I am concerned, it is not fair to them, they are not being paid for it, and it is also not necessarily feasible. That is what happened in the sticker system, and it sounds like that is what you are proposing again.

DR. HUBER: Maybe I am misusing the word "enforcer." What we are relying on is the system will identify is there a negative pregnancy test

done that meets the time window criteria. The pharmacist's role in this will be to make sure that the patient has indeed qualified within the system.

The difference is in the sticker system, the sticker represents a physician attestation that a pregnancy test was done. So, you have two potential sources of error. One was upfront, the physician on the sticker, the second was the pharmacist in looking at the sticker.

We are not eliminating all potential sources of errors this way. What we are trying to do is, one, at least eliminate the upfront one because there has to be a laboratory test result, which overrides, shall we say, the physician attestation on a pregnancy test, and on the back end, we are trying to make it as simple as possible for the pharmacist, so he doesn't have to interpret data, he gets a yes/no answer.

DR. STROM: Again, how does the data, the hard link that you talked about of the pregnancy test, get into the system?

DR. HUBER: What we are envisioning is

that there probably has to be a two-step process to that, because, one, we had talked about having it go directly from the lab to the system. One of our concerns was if there was a pregnancy test, we really think the physician needs to know about it.

So, we think the pregnancy test needs to go via the physician, but there probably, in order to close this loop of the hard certification, there needs to be some way to enter either the information directly into the system from the lab, or that there is a fax copy or something to follow up.

DR. STROM: I guess my own preference would be to reverse it. Certainly, you want to make sure the physician knows, but I wouldn't have the system dependent on the physician. I think the hard data should go directly to the registry, and while you are at it, notify the physician, so the physician knows about it, so that there is a positive, so there really is a hard link.

My second question is when I read through the description, and we heard you present it

yesterday, I was a lot less reassured. Now, hearing it in the context of the S.T.E.P.S. program, it sounds much closer.

Can you nail down for me what the differences are between this and the S.T.E.P.S. program, and in what way is it not the same as the S.T.E.P.S. program?

DR. HUBER: S.T.E.P.S. does not require a certified laboratory test. It is a physician attestation into the system.

Secondly, S.T.E.P.S. requires weekly blood tests the first treatment. We are not proposing that. The third difference--that is the two differences. The third element that will come up, the difference is in the distribution of the product, because we are in a multi-source environment versus a single source environment. That is one of the issues we are going to have to kind of sort out, because that is novel for this approach.

DR. KWEDER: I would add the other differences are S.T.E.P.S. enrolls everyone. This

would only enroll female patients.

DR. HUBER: No, our current proposal includes males and females.

DR. KWEDER: You didn't say that before.

DR. HUBER: I am sorry, I apologize.

DR. KWEDER: And you also don't have the follow-up survey, correct?

DR. HUBER: Our focus on this was on the interventional elements while the patient is getting treated. With regards to the follow-up survey, the other point I would like to bring up on the mandatoriness of that, it kind of comes back to the question that was raised yesterday about the 30-day follow-up.

The problem with any follow-up survey is we can say it is mandatory, but the ability to enforce it is almost nil, because if the patient doesn't have to come back to receive a product, they don't have to do anything.

So, we can make them sign and say it's mandatory, but at the end of the day, the reason the patient is going to show up for their blood

test and answer the questions on the IVR is because if they don't do that, they don't get isotretinoin.

So, one of our concerns was is any of those follow-up surveys, you are going to get back into significant issues of will patients participate. We see this as focusing much more on the intervention, the pregnancy prevention aspects.

We think we should be able, with this approach, to get data, the data you are looking for as part of the ongoing intervention during the treatment.

DR. GROSS: You just said that males will be included. Are you going to recommend male contraception, too?

DR. HUBER: With regards to male contraception, we do not recommend male contraception. You received the copy of our report. That report has been submitted to the FDA in I believe 2001. We have done multiple investigations, both clinically and preclinically, and we do not see evidence of a risk from a paternal exposure to a female.

I would like to remind you the drug is not a genotoxin, so it doesn't have an effect on sperm, so the only risk would be transmission via seminal fluid. When we have investigated, the exposure from seminal fluid is one million times lower than a single 40 milligram dose, so based on that data, we don't see a risk.

When we reviewed the case data, we have not seen--we have seen isolated malformations, but please remember malformations do occur in the population, but in the 20 years out there, we have yet to see a paternal-exposed pregnancy in which the triad, the classic triad of a retinoid embryopathy, as described by Lammer [ph], has occurred.

DR. GROSS: Are there any comments from the generic companies?

MR. POLLOCK: Thank you.

A couple of things I just want to point out, so everybody is just aware of it, is the generics and the brand name companies first got together to start talking about this on December

10th, when we were called in to the FDA.

From an operational standpoint, people had mentioned the fact that we might not have the details worked out. Well, we don't. I mean it has been amazing to get to this point, I think, with five different companies, six different companies in this period of time.

So, we are thankful for all the cooperation, but some of the questions you pose, we might not have answers for because we haven't been able to fully consider them ourselves, and we have learned a lot, I think, from the Advisory Committee comments and things of that nature.

To harken on Dr. Kibbe's comments, this is a fairly complex program. We have to again I think just recognize the impact on the physician, the patient, and the health care system that is going to be providing these things, because we don't want to force people outside of the area.

So, I would just like you to always kind of keep that in the back of your mind.

The other issue is--and I raised this

yesterday--Marty described a system where the educational component and the responses were going to be tied into this yes/no determination. This was one of the things we asked for your input on.

If there is a patient that has an inappropriate response during the educational component, but has a negative pregnancy test, we would like your advice on what to do with that patient.

Should the patient receive the drug and perhaps automatically a letter be fired off by the registry system itself back to the physician indicating this is a high risk patient, here is the questions they answered wrong, you need to counsel this patient?

If the patient fails the second time, maybe that would be the no drug contingency. But we would like you to also consider that, as well.

Those are the issues that we think are very important to keep in the back of your minds when we are evaluating where we are going to go and how we are going to get there, and whether or not

it would be appropriate even to move in a stepwise program--that was kind of a pun, I guess, I didn't mean stepwise--a uniform program over the course of time.

Thank you very much.

DR. GROSS: Thank you.

Dr. Whitmore.

DR. WHITMORE: I would remind Dr. Huber that 32 percent of the pregnancies that occurred, occurred during that last month after treatment with Accutane. I think somebody had mentioned that after one month, it is okay to get pregnant, so those issues are not important.

But coming back to this, 32 percent of the pregnancies did occur in that 30 days after Accutane therapy, which is a critical period, and we still have no mechanism by which to address that as far as these women coming back.

I would suggest maybe some type of monetary gift to patients when they come back at one month or something and have their pregnancy tests done, but I think that really does need to be

addressed considering it's a third of the patients who do get pregnant.

One other thing, too, about the computerized system and everything, in terms of the logistics of the pregnancy test, getting to the pharmacy and everything else, this is going to be very expensive. Robyn Shapiro asked who was paying for the Celgene program, and the answer was Celgene, but that's not true. That's patients and insurance companies or whoever. So, patients are going to be paying for this program whatever it is.

I would suggest that every patient who does receive a prescription with a sticker has to come back to the office to pick that up after the pregnancy test has been done. Thus, we can give them a copy of the pregnancy test, they can take that to the pharmacist with them.

That will eliminate any embarrassment about a positive pregnancy test, going to the pharmacy without the physician knowing about it, the patient knowing about it, and it can all be hand-carried to them.

The pharmacy is well aware of the Accutane Pregnancy Prevention Program, the stickers, and the whole bit. All you have to do is add in a pregnancy test required to fill the prescription for it, and then you don't have to have this expensive program.

DR. GROSS: Robyn Shapiro has a question, and I have a question for her. As the ethicist on our committee, do you have any comments you would like to make in that regard as far as the child or the mother?

MS. SHAPIRO: I do, and I was going to ask you to ask me that, but, first, can I ask my question, my other question?

Getting back to the expensive interaction program, which is along the lines of what I had suggested just a little while ago, to ensure, I hope--I mean it is still pretty vague, so whoever, Roche or generics, whoever wants to answer this question--what would you be looking for?

Would you be looking for both comprehension, as well as suggest compliance or

noncompliance, and then, two, if there is a problem with respect to one or another, my own response to the request for input from us about what to do, would be to circle that back to the dermatologists, both to enhance, enrich, and inform that relationship, and because I think it would be inappropriate for a computer or a program, or whatever it is, to countermand an order that had been submitted from a doctor on account of the interaction with the program.

DR. HUBER: With regards to your question, the first draft of questions will be modeled somewhat analogous to the S.T.E.P.S. program current questions. Once again, we are trying to build on a program that is already in place, and they already have an IVR interaction for questions.

Clearly, this is a relatively new science in doing this on testing for compliance for pharmaceuticals through IVR. Anything that is learned from that, we would appreciate, and anything that this committee has to say as recommendations on how to do those questions

better, we would be interested in knowing.

With regards to the latter part of your comment, that is something that has always bothered us is at the end of the day, the physician is ultimately responsible for the education and information for the patient.

We are now adding in, shall we say, a little test along the way to see if the patient really got it, and also reinforcement. That is difficult for us, and we are struggling with that whole concept. When we look at the S.T.E.P.S. as the model, that is what they are doing, and we are basing that on that approach.

There is not a lot of other choices of things that have been modeled previously, and kind of using the basic thoughts of we don't want to get too experimental here. That is the one approach that has been tried in a population.

MS. SHAPIRO: Again, personally, I think it's okay to do a little test as long as the remedial response is put in the lap of the doctor, and not you.

DR. HUBER: Yes, agreed.

MS. SHAPIRO: Your request, and you know, as a disclaimer, like any good lawyer would do, I guess, this may confuse more than help, but we are struggling with how can we accept that we are not going to have zero pregnancies, and if we do accept that, what number is good enough.

In order to do that, we need to weigh and balance, of course, the benefits of the Accutane to the patient, and I think we are probably all pretty convinced that there are significant benefits, to the harms.

When we get to the harms, we have really potentially two individuals, as well as society, to take a look at. We have the potential harm of the woman who has to raise an impaired--this is if we fail to prevent pregnancy 100 percent--has to raise an impaired child, and the life of the impaired child, and the burden or the harm to that child of that life, and the burden to society.

If we are successful 100 percent in preventing pregnancy, no one has those burdens. If

we are not, the woman has a choice. We could, but I hope we don't, get into a conversation about abortion at the moment, but she does under the current state of the law in the country have a choice about whether to continue with that pregnancy or not.

If she chooses to terminate, then, she has the burden of going through that, which clearly is significant, as well. The child is spared, there is no child, so that harm goes away, as I suppose does the harm to society to a certain respect.

If she chooses not to, can't, won't have an abortion, then, she bears the burden of going through the pregnancy and raising an impaired child. In response to that, if we are good at what we are trying to do, which is to fully inform and provide a way for her to avoid that, in part, that is her responsibility and then her choice.

But she has been forewarned, the child, on the other hand, hasn't. So, in some ways, one might see the harm to the impaired child as being more significant than the harm to the woman who is

in the position of having to raise the child.

How do we place a value on or get our arms around the burden to the child? What does that mean? What is the importance? What is the gravity of that? That is where we really have a problem.

If we analogize to what courts have done in wrongful life lawsuits, and typically, these lawsuits are brought when there is a failure to inform about a potential genetic test or something like that, and the woman is deprived of that information, so doesn't have information about which she can base an abortion decision on.

An impaired child is born, and the child will then sue and say, doctor, had you only told my mother about these options, I wouldn't have been born, but I am, and therefore I want bunches of money because this is a terrible burden to me.

Many more jurisdictions than not will not act on the lawsuit, will not provide that child any recovery because the judge will say you are putting me in the position of having to say that any life, while impaired, is worse than no life at all,

because the option, the alternative in your situation, you plaintiff child, is that you would not have been born. I will not say that not having been born is more valuable than life while impaired.

This, to me, just shows the difficulty in getting our arms around the nature of the harm that we are trying to prevent here, which makes it all the more important that we do a really good job in preventing the situation in the first place, so that we are not left weighing and balancing this abortion decision, and what if, and what if not, and what is the value of the harm to the child that is born.

DR. WHITMORE: May I ask a question?

DR. GROSS: Yes.

DR. WHITMORE: I am sorry, of Robyn Shapiro. What do you think of having that information, just the gravity of that information with regard to having an impaired child and raising that child if indeed you got pregnant when on Accutane or otherwise having to have an abortion

because of the pregnancy occurring during Accutane therapy, what do you think of having that on the consent form just to give the patient the gravity of what we have been discussing here today?

MS. SHAPIRO: If that were doable, I think it would be great. I mean I am all for more information again mostly, so that we can ensure a real reasoned decision upfront, and therefore compliance with what we are urging them to do, and not have to grapple with these horrible sensitive, unanswerable question later.

DR. CRAWFORD: Thank you. I have just a few comments about the patient registry and a question about the patient process.

With respect to the registry, I think one of our responsibilities is to recommend advice with respect to what entity should be responsible for registration and maintenance of a registry if it existed.

My opinion is that I would agree with what others have said, it must be a consolidated system, one program meaning there will be the need for

negotiation and agreement as to the components of it, ideally administered by qualified, third-party vendor or contractor.

In addition to helping to achieve program goals, that would help allay any concerns that anyone might have about potential promotional use, which I am sure is not the goal of any of the sponsors, but sometimes there are questions about that, not on the ethics part, but that process would also include what information should be collected, such as things Dr. Shapiro and others were saying, and how the information of the registry would be used to prevent embryonic exposure.

My question, living in Chicago, I know that many languages are spoken by patients and their practitioners. My question is if the patient cannot comprehend English or Spanish, would they be excluded under the described program from receiving the drug or would the physician be able to work with those patients on a case-by-case basis.

DR. HUBER: We have discussed English and

Spanish, we have not discussed any languages beyond that at this point in time.

DR. CRAWFORD: I am sorry. To make my question clear, I am not expecting the program to necessarily be able to adapt to any language as opposed to would there be a different mechanism, more one-on-one with the practitioners if it was believed the patient needed the drug therapy and couldn't understand English or Spanish.

DR. HUBER: I don't know the mechanism. We would be happy to hear if the committee has any recommendations on that.

Committee Discussion (Continued)

DR. GROSS: I am trying to move along here, and I think we can call on the next few people that have some questions, but I am beginning to get a sense that we are in the process of answering Question 3.

I was asked to take a vote on the slide on the bottom of page 3. Let's just do that one and then we will talk more about the particular program.

The statement on that slide says, "Should we continue the current risk management program without additional tools?" I think I know the answer of the group, but I think each person is going to have to declare themselves.

So, let me read the question again, and then starting with the sated Mr. Levin, should we continue the current risk management program without additional tools?

If you vote no, that means we don't want to continue the current risk management program.

Mr. Levin.

MR. LEVIN: Arthur Levin. No.

DR. SAWADA: Kathy Sawada. No.

DR. VENITZ: Jurgen Venitz. No.

DR. STROM: Brian Strom. No.

DR. BERGFELD: Wilma Bergfeld. No.

DR. RAIMER: Sharon Raimer. No.

MS. KNUDSON: Paula Knudson. No.

DR. BIGBY: Michael Bigby. No.

DR. HONEIN: Peggy Honein. No.

DR. COHEN: Mike Cohen. No.

DR. WHITMORE: Beth Whitmore. No, but not with the proposed plan.

DR. GROSS: We are not there yet.

MS. SHAPIRO: Robyn Shapiro. No.

DR. EPPS: Roselyn Epps. No.

DR. SCHMIDT: Jimmy Schmidt. No.

DR. CRAWFORD: Stephanie Crawford. No.

DR. GROSS: Peter Gross. No.

DR. WILKERSON: Michael Wilkerson. No.

DR. RINGEL: Eileen Ringel. No.

DR. VEGA: Amarilys Vega. No.

DR. DAY: Ruth Day. No.

DR. KIBBE: Arthur Kibbe. I am forced to say no, but I really would rather have had a vote between this plan and another one, so I had something to compare it to, because this is better than nothing.

DR. GROSS: We will meet your needs momentarily.

DR. GARDNER: Jackie Gardner. No.

DR. KATZ: Robert Katz. No.

DR. SELLERS: Sarah Sellers. No.

DR. GROSS: That is about as unanimous as you can get. There are some more questions that we will then apply to the fact that we are going to recommend something different.

Michael Cohen.

DR. COHEN: I guess touching on what Dr. Strom mentioned earlier about the enforcer and workloads, et cetera, and where they might lie, do you have plans if an enhanced program is implemented to interact with the medical and pharmacy community, get feedback?

A few times people alluded to failure mode and effects analysis. Do you have plans to conduct that and involve practitioners in that process? I am asking that of industry.

DR. HUBER: One of the first steps would be the establishment of a scientific advisory board, which we have had for all of the previous risk management programs. We would intend that that would include stakeholders in the program, as well.

There would need to be some interaction

with the dermatology community, the pharmacy community, et cetera, but we would see that as something done in parallel to the scientific advisory board as part of that activity.

DR. COHEN: And the concept of failure mode and effects analysis? In other word, developing this process, flow diagram a little bit further and then going back and trying to determine where failures might occur in that process, and then come up with a way to prevent those failures.

I think you do need an advisory group to do something like that.

DR. HUBER: Yes.

DR. GROSS: I have been advised to try to keep the discussion among the committee, and not go back to industry for answers unless it is absolutely necessary.

The next person, Dr. Honein.

DR. HONEIN: I am very concerned that they don't plan to do a follow-up survey as a component of this for a couple of reasons. One, I think during the interactive process to get the

prescription, the really only alternative is for the patient to give the best case scenario plan, to things like what do you plan to do for contraception, both socially desirable responses, and maybe their intentions, they don't get followed through upon, whereas, a survey after the fact can get at what did you really do, during the course of treatment.

While some people may still give socially desirable responses, at least you have the opportunity to let them sort of look back on it and provide the best information.

My second concern is since we are already under-ascertaining pregnancies, that this would increase the under-ascertainment. I think if a woman diagnoses her own pregnancy during the course of treatment, she is not going to go back to the system for the next refill. She is going to go to a separate health care provider that deals with that pregnancy, and where does the system find out about this.

The follow-up survey is one more

opportunity to locate that. With that regard, I was wondering if we could refresh our memory on what proportion of the pregnancies we know about now came from the follow-up surveys, after the fact.

DR. GROSS: Does FDA have any information on that?

DR. KWEDER: Can you state the question? I got all the beginning, but the question again.

DR. HONEIN: Of the pregnancies that we know about in total, exposed to isotretinoin, how many of those do we know about because of the follow-up survey rather than another mechanism?

DR. TRONTELL: As Dr. Pitts described yesterday, the majority of reported pregnancies to the Agency come via the manufacturer. The minority--we can pull up the slide to give you the percentage--but my recollection, it is about 20 percent come by the follow-up survey.

DR. HONEIN: Right, but I think that would be a big loss to lose 20 percent of the pregnancies that we know about now by not doing that follow-up.

DR. GROSS: I think when we come up with a final plan, you can put that in as a suggestion to be part of the plan.

Dr. Gardner.

DR. GARDNER: In Dr. Huber's response to Dr. Strom, there was something of concern to me, and that was that the pharmacist would be asked to interact with the registry system in order to further document the negative pregnancy test.

I think this builds in another potential for failure in that the pharmacist now has a yellow sticker that we have discussed, that has, in theory, the physician's documentation that there has been a negative pregnancy test, whether it does or not.

If we now ask the pharmacist to take that and do an additional step, and that is to double-check that information against the registry, which is what I thought I heard from Dr. Huber, then, I think that we are building in another point of potential failure there, some 55,000 pharmacies in the U.S., and many of them are high volume.

Yesterday, in the FDA presentation, we learned that of the places where there were problems with stickers coming incorrectly, they tended to be to high-volume pharmacies and to rural pharmacies. My guess is that adding an extra step in those circumstances where we are already seeing where some problems lie, would ask for trouble.

So, I would suggest that whoever mentioned that the pregnancy test result loop should go back to the physician who then attests on the sticker or something else, so the pharmacist has one thing to look at, and that is it, I think would reduce that potential.

DR. GROSS: Mr. Levin. Mr. Levin went out for a snack.

Dr. Kibbe.

DR. KIBBE: As soon as Mr. Levin comes back, I will give him a chance to jump in.

I have just a couple of observations about what we have been doing for a while. First, you cannot test quality into any system, and the pregnancy test that we do prior to initiation of

therapy assures that the patient at least is not pregnant when they start.

Pregnancy testing during therapy seems like a QA test to me, and it's a QA test of whether the patient is behaving appropriately in terms of not getting pregnant.

That is never going to change the patient's behavior and prevent the pregnancy, it is just going to tell us when it happened, and then what do we do about it, and it is my impression that by the time we find out, the damage is done and we have to do all sort of other things, so that is not even helping us get to what we want, which is no pregnancy, it is just testing for it, and testing just to prove that something is going wrong is just--an awful lot of what we talk about around here is changing behavior, but everything I hear them talking about in the program is changing the behavior of the physician and the pharmacist, and what we really want to do is what?

It is change the behavior of the less than 1 percent of women who, when they are counseled on

how to behave during taking this drug, somehow don't get the job done. So, that, we need to focus on a little more.

I wanted to get back to my ethicist here, because I know that some of my ideas, I admit freely that they might sound draconian, but if the result is draconian, then maybe the cure is draconian.

So, would it not be a lesser harm to society and to the individual if we require anybody of childbearing age who wants to take this drug to have a permanent IUD put in before and removed two months after, so that we close down the loop.

If we can identify people at risk, wouldn't that be a better way of maintaining the zero pregnancy option or at least getting close to zero pregnancy than trying to do a lot of things, and education never works 100 percent of the time.

MS. SHAPIRO: From a theoretical point of view, you are probably right, or, you know, give a shot or something like that. The problems that we encounter are, first, what are the risks or side

effects of that. I don't know.

Second, in this country, in the law and in ethics, we tend to accord reproductive decisionmaking a lot of latitude in terms of freedom of choice and privacy, and so forth. So, that might--I am not saying that you couldn't do it--but I think it would not be an easy sell from a PR point of view.

DR. GROSS: Mr. Levin.

MR. LEVIN: Two things. One is a caution about loading up informed consent documents with lots of information and the assumption, which I think is disproved in the literature, that informed consent does what it is intended to do. I mean I think there is a lot of stuff that has been written and a lot of taking a look again at how the informed consent process works, as well as how IRB processes work.

The other thing I would like to reiterate what I said before the lunch break, which is it seems to me that we may all have our personal ways of sort of trying to tweak this system, but they

are not based on any evidence.

I would once again emphasize that we sort of have a responsibility to patients taking this drug to make decisions based on the best possible evidence that they are actually working to prevent the outcomes that we are committed to preventing.

So, I think we really ought to look at the existing programs and only nibble at them with changes if we believe there is something about them inappropriate to this particular population and drug.

But I think it is a good place to begin and I think Roche has constructed a program that comes pretty close to sort of borrowing a lot from S.T.E.P.S. and a little bit perhaps from the other program.

I just want to emphasize that it's evidence based and that we have data that tells us that that approach may be an effective approach, not that it can't be improved, and to suggest again a hypothesis of what we would like this to look at, that have no evidence is simply going to delay this

process even more and mean that more patients will be hurt in the intervening years until we get data to prove whether our suggestions were workable or not.

DR. GROSS: Art, since you are moving us in that direction, the other part of Question 3 is what would we propose. So, why don't we consider, let's say, accepting the Roche Risk Management Program and decide whether there any additions that need to be made to it, such as making sure that males are included and what you want to do about making a survey mandatory, et cetera, if we could perhaps direct our comments to those issues.

There are a couple other people that wanted to comment. Dr. Bergfeld.

DR. BERGFELD: I was only going to address the foreign-speaking individuals who might need Accutane. I think they need to be handled on a case-by-case basis. I think most of those individuals, depending on their geographic location, might be referred into tertiary care centers where there are interpreters, and

frequently, in some of the rural areas, there are foreign-speaking nurses, so we are taking care of these people at the present time.

DR. GROSS: Sarah Sellers.

DR. SELLERS: I am sorry, are we on the actual Question 3?

DR. GROSS: We are on page 4, the top slide.

DR. SELLERS: My comment was given the goals of the pregnancy risk management program, to ensure continued access to a drug that has been proven to be effective in patients who suffer from severe nodular acne, is there a model or is there a mechanism, or indeed does the FDA have the statutory authority to restrict the use of the drug to its labeled indication, and then provide a mechanism for treatment IND to off-label use.

DR. GROSS: Does anyone from FDA want to answer that?

DR. KWEDER: Yes, I can answer that. We do not regulate the practice of medicine, and off-label uses generally have historically been

considered practice of medicine issues.

What we usually do when we are trying to influence the practice of medicine is we restrict the labeling or we impose other kinds of programs, such as the ones that have been discussed today, to try and minimize a use that is not consistent with labeling.

So, in terms of ensuring, for example, if you look at one of the examples presented today was Thalidomide. Thalidomide is not approved for the treatment of any oncologic condition, but the vast majority of uses are for treatment of different kinds of cancers, particularly multiple myeloma.

We have not found that we are in a position to be able to restrict those uses.

DR. GROSS: Dr. Ringel.

DR. RINGEL: It is sort of hard to get anybody's attention deep in the recesses of the table, so I have actually collected quite a few. I will try to go through them quickly.

One is that people need to remember that there are practitioners who are in rural areas and

their patients may live very far away, and I would ask, when you make the rules, please don't make the rules so that patients need to come back the next day to pick up X or Y, you know, the pregnancy test results, the prescription. Don't make them make trips just for silly things like that.

I would think fax could be an option for some of those things, faxing a prescription with the sticker on it to the pharmacy, something or other. I think that is an unreasonable burden.

The other thing is that I think the first pregnancy test is problematic because the value of a negative first pregnancy test is basically worthless if the patient has conceived within the week before that test.

The two ways the FDA has decided that that won't happen is, number one, to make sure the test is taken during the menstrual period, and, number two, to make sure that they have been on two forms of contraception for a month before that test.

We have done nothing to address that those have happened, so I have these proposals, and I

think actually that happens a lot. I think that people who, for example, have been on birth control pills, why make them wait a month to use a second form of contraception, how silly, except it is not silly. I think that actually people go on Accutane in less than a month after that first visit quite often.

So, what I would suggest is two things. First of all, the pharmacist, when he or she checks the prescription to make sure that a pregnancy test is there, can also make sure that it has been a month since the patient registered, because it needs to be at least a month between that registration date and the date they have picked up those pills to know that they have had a month to be on two forms of contraception.

The other--and I am not sure if this would work, but it is just an idea--people want to get on this stuff, they don't want to wait until they have their menstrual period. Would it be possible to do urine pregnancy tests and then do a dipstick for blood assuming that that specimen was done without

a tampon? You would know the patient is menstruating, at least you could verify that.

There was another issue brought up about nobody is addressing how to keep people from getting pregnant while they are on the drug, and it seems to be an issue of education. How do you educate the patient to both understand the issues and to believe that they really can get pregnant just on one form of contraception or none?

What I would suggest there is that the FDA fund some educational studies. There are various ways that I can imagine to try to convince people that it might be a good idea to be on two forms of contraception, but I can't tell you which one would work, and I would think that funding small studies to find out what educational methods are really most effective might be a quick and cost effective way of doing it.

Last but not least, given the last discussion, I am not sure this would work, but seeing the three people from the community who testified today, the man who had birth defects, and

those two poor women, it is very difficult for me to justify giving this drug to any acne patient who does not have severe scarring, either nodular or at least papular, pustular acne.

I know, and you know, that many of the prescriptions for women who are using this medication, are used for those other purposes. If that weren't true, the number of males being treated would vastly outweigh the number of females being treated, but that is not the case. Almost by definition, the females are being treated for less severe acne with Accutane.

I think that Dr. Wolfe's suggestion about faxing photos may not be the worst thing in the world. Almost everybody has a digital camera, it would be easy to do. Frankly, I don't think that you would even need to make a decision, oh, well, this guy has severe enough acne or that guy doesn't.

I think if people just had the responsibility of knowing that someone else was going to look at those photos, sort of knowing that

big brother is watching, I think that the rate of Accutane use in females would go down dramatically.

DR. GROSS: Dr. Ringel, you have brought up a number of excellent points that we will have to consider when we come up with our final plan.

I am going to take two more comments and then I am going to ask you to consider voting on Roche's plan as an initial ingredient of the plan, and then come up with other areas that you think should be added to the plan, if that is your pleasure.

The next two comments will be Dr. Strom and Dr. Day.

DR. STROM: Thank you. In follow-up of that, I very much agree with the idea of Roche's plan as a core, but share Jackie's concern, and want to follow up on Jackie's concern and the comments I made before, that the plan is still counting on the pharmacy essentially to be the enforcer.

It is the pharmacy that has to do the work, that has to check whether they are pregnant

or not, that has to sign into the registry if that is the case, and get that information. You are talking about tens of thousands, 50,000 pharmacies you said?

DR. TRONTELL: 55,200.

DR. STROM: 55,200 pharmacies with many more pharmacists. It is a system which is bound to break down. It is also a system where people are not being paid for their time, and the pharmacists are now doing it out of good will, but, in fact, are very busy and very stressed out, and you are adding more to some very busy people.

So, I would argue that that plan should be augmented by a system of a more selective system of pharmacy dispensing. It can be multiple options, and I would recommend multiple options, a centralized system whereby you could use mail order, for example, and/or a specialty pharmacy.

There is increasing use of specialty pharmacies where pharmacists are paid more to provide a particular kind of care, and I would have the registration system basically be a

certification of specialty pharmacies, that these pharmacies would get paid extra for doing this, but would have the obligation and expectation of doing it accordingly.

So, for the patient in a rural area, there would be a centralized system that they could get it from a mail order system. Many people might use the mail order system indeed, but I wouldn't necessarily think we need to restrict it to just a mail order access.

I think the use of what is increasingly common in terms of specialty pharmacy makes sense. So, let's make sure that the person who is the enforcer has a vested interest in doing the enforcing and is paid for that interest, because right now that is not happening.

DR. GROSS: Dr. Day.

DR. DAY: In the component that tests patients' knowledge, I think more work needs to be done. Everything that I have seen presented is about being able to give back information that is already provided, so that factual knowledge or

repetition even.

I think we need to have more complete comprehension, which would involve making inferences and perhaps giving scenarios, say, if you did this, and then that, would it still be all right to take the medication, and so forth. So, I think a more careful look at the comprehension component.

I guess I will save the last part of my intended comment for when we add additional tools.

DR. GROSS: Let's take the Roche handout on pages 82 and 85 that I referred to before. Let's take a vote on whether or not we would agree to propose that as a core program that would apply to all people who are candidates for Accutane or the generic equivalent, so this will an addition to that program. The same program applies to those taking generic isotretinoin, as well as the Roche product.

Stephanie.

DR. CRAWFORD: Thank you. I just need a clarification with respect to I was looking at the

components because there are certainly some areas that are very good and some that I don't think are sufficient, need to be added to that, so we said, you know, we wanted modifications initially, such as I just don't want to be misunderstood if I voted yes in terms of the components of the system.

There are certainly things I would want changed, such as where it said "centralized system," I want that specified as one consolidated system for all the isotretinoin sponsor manufacturers.

Also, we will need to address the issue of a male patient registry. Is that part of it, or is right now we are just looking at females, et cetera?

DR. GROSS: The program is certainly going to be added to from the initial. I don't want to make things too confusing and vote on too many things at once.

DR. STROM: Peter, as a point of order, maybe it makes sense just to have people go around, one by one, vote on this as a core, and for each of

us to describe what we would add to the system in the process.

DR. GROSS: As they are voting.

DR. STROM: As they are voting.

DR. GROSS: Yes, that's fine.

Mr. Levin.

MR. LEVIN: My understanding from Roche's presentation is that this is male and female, am I correct? Okay. I would certainly vote yes in favor of this as a core, and I think the most critical addendum is what Brian just described as some sort of centralized and specialized dispensing program added to this core.

DR. GROSS: I am going to make a list of the ideas that you are proposing be supplemented, and then we will talk about them. So, it's the Roche program, it applies to males and females, and the Roche program will be used by Roche and by the generic manufacturers.

DR. HONEIN: Is it mandatory?

MR. LEVIN: Absolutely.

DR. GROSS: Is what mandatory?

MR. LEVIN: Yes, I mean Roche's proposal is a mandatory program.

DR. GROSS: Right, men and women and any other sex.

DR. SAWADA: Kathy Sawada. I would agree with this Roche program as a core program, mandatory, applying to both male and female. I still think that we need to work out a few things with regard to pregnancy testing and dissemination of that information. I will leave it at that.

DR. GROSS: Good, fine.

DR. VENITZ: Jurgen Venitz. I am in favor of the core program, as well, again with the stipulation that what is listed here is mandatory. That includes registration of physician, patient, and pharmacy.

I do think more effort needs to be dedicated to the educational component to make sure that it is not just an exercise in futility, but there actually is learning occurring, and that the learning outcomes are assessed, not the factual repetition of knowledge.

I am also concerned, as was discussed before, about patients past their treatment course beyond the 30 days, that there should be at least attempt to systematically follow up on those patients.

DR. GROSS: It is understood that in this program, registries are mandatory for physician, patient, and pharmacist. Pharmacy? All right. We may have to discuss that.

DR. STROM: Brian Strom. I am in favor of the Roche program as a core program, again, both genders. I think the two particular things I would add is a mandatory follow-up survey and the limited dispensing by a centralized dispensing system plus specialty pharmacies.

DR. BERGFELD: Wilma Bergfeld. I am also in agreement to the Roche program. I would like to beg for the physicians that have to evaluate the patients, that the packaging of the educational materials, the consent forms, the pregnancy recording forms, the flowsheets, the stickers, be simplified for easy use and interpretation.

DR. RAIMER: Sharon Raimer. I have some real qualms about the program as it is outlined. I think it is going to be a very expensive way to be sure that patients have negative pregnancy tests, and I think you could get at the same thing by having the pregnancy tests sent to the pharmacy or having yellow stickers, have a box where you actually have to put the date of the last negative pregnancy test on it.

I would be more for it if there were more of an educational component. I just don't see that this gives the patient that much of an education because they will learn the right answers in order to be able to get the drug to answer the questionnaire.

So, I think the number of phone calls it is going to require, and the expense that it is going to entail, is not justified in its present form.

DR. GROSS: So that is no vote?

DR. RAIMER: That is a no vote.

MS. KNUDSON: I will vote yes for the core

program. I would like to also understand the privacy and confidentiality that goes along with the registry and urge that indeed we build in sufficient safeguards for that.

I would like to also add would it be possible to send out a newsletter, to draft a newsletter centrally, send it out periodically to the patients who are on the drug, reaffirming a lot of the issues that are necessary for their appropriate education.

Thirdly, I would like to be absolutely certain that we have very tight inclusion criteria before dispensing the drug.

DR. GROSS: Thank you.

DR. BIGBY: Michael Bigby. I actually share Dr. Raimer's reservations about the program, and I think a program needs to include a mechanism for tracking and evaluating women who get pregnant.

I think it needs to capture and insist, as Dr. Ringel said, that patients are, in fact, using two effective forms of contraception while they are taking Accutane, and I also think it is essential

that a plan be added to collect data on that last month after Accutane has been discontinued.

DR. GROSS: So, I understand the things you think should be added, but is your vote a yes or a no as this being a core?

DR. BIGBY: No.

DR. GROSS: Dr. Honein.

DR. HONEIN: Peggy Honein. I would vote yes to this as the core for the program, but I think it is critical to have a follow-up survey both to get better quality assurance data about what is working in the program and what is not, because I think there will be needs for modifications down the road, and we need to have the best data possible to make those decisions on, and also as a tool to better ascertain pregnancies.

I would also like to see an additional plan for what other mechanisms can be used to get closer to the number of pregnancies that are actually happening and do more complete ascertainment of that.

DR. COHEN: Mike Cohen. I am for the core

program. I am against severe restrictions in pharmacy access. I think, you know, all in all, we have seen pharmacists have been doing a pretty good job with it. I think there could be a voluntary registration of pharmacies or willingness to participate in it.

I also wish there was some way to indicate in the registry whether or not the patient has severe cystic acne. I realize that you can't restrict the prescribing, but perhaps that still could be included in some way.

DR. GROSS: So, your last comment goes to the entry requirements, which we should address after we are finished voting. Okay.

Dr. Whitmore.

DR. WHITMORE: Beth Whitmore. I vote no. I don't think this will prevent pregnancies any more so than a sticker and a pregnancy test presented to the pharmacist. I think that it should be mandatory that a physician reports pregnancy to the FDA and also to the drug company when it does occur, and I think that needs to be

said, that that is mandatory and prosecutable if it is not done.

I think that should be in the patient consent form that the physician will inform the FDA and the company if the patient does become pregnant during therapy, and there is something else that I am forgetting--oh, the video.

The video has been lost in terms of I have never seen it in our office. I was part of an Accutane educational program, it's a one-day seminar, and saw that video. It is my fault that I haven't obtained the video and given it to every single patient, but it is an excellent video, and patients are more visually oriented than they are reading all these documents.

I think that video should be given to every woman. They can view it at home, and if not, they can view it somewhere where they can get a VCR.

DR. GROSS: Robyn Shapiro.

MS. SHAPIRO: I guess I vote yes with the proviso, some which have been mentioned, that we

assure that there is something that is done with respect to the last 30 days, that my own concerns about the interaction in terms of identifying lack of understanding and lack of agreement or likelihood of complying have some appropriate resolution, that that loop be tied.

Also, that we have some assurance that we are going to be collecting data. I think that we have suffered here in the last two days from lack of data, and hopefully, this will help us get that and maybe we should even think about a sunset date for this particular plan to be re-evaluated in light of data that is collected to see if it is really doing anything although that may be implicit, I don't know.

DR. EPPS: I vote no.

DR. SCHMIDT: I vote no with a oak leaf cluster because I think that this is going to be unbelievably expensive and I think some of these registries, like this other program for Thalidomide, is a nightmare.

I think that what Boni talked

about--excuse me, Dr. Elewski--I agree with that, that we should have a survey, the survey should be mandatory, and then one of the things is I really wonder whether we ought to simplify this thing.

To me, I think one of the scariest things with males is sharing their medication, but as far as registering males other than that, I don't know that we ought to really have them in the system.

DR. CRAWFORD: I vote yes, a qualified yes with respect to the core components. The additional thing I would like to ensure, that it is a consolidated, single system. The evaluation methods proposed I believe are insufficient, and there needs to be improvements in evaluation methods and the results used for program modification as necessary.

Also, I believe there should be some consideration of a case-by-case basis where some patients simply may not be able to do this, such as we talked about, perhaps with language difficulties.

I am sorry, sitting between two physicians

for two days has made my own handwriting really bad. I think I wrote the need for possible recertification of the practitioners or representative from the pharmacy either annual biannual, or some mechanism, because one time may not be enough to just reinforce the need for all the steps.

DR. GROSS: Peter Gross. I vote yes.

DR. WILKERSON: Michael Wilkerson. Having sat here for two days, I am astounded at the lack of information and forethought put into after this drug having been on the market for 22-plus years, that we don't have any better way of dealing with this problem.

I don't see that this is an improvement over the current system. I think there is something better out there, but to experiment by using an entire country at once is folly. What should have been going on, and has not been going on, are pilot studies to determine what is the best way to do this.

This program does not, in my view, add

anything but more layers of complication that may actually lead to less compliance than what the current program is, and I wish the manufacturers would get together and solve this problem on a small-scale basis before we start trying to implement a national program.

I would also ask that industry hopefully come up with compounds that we don't have to deal with this particular issue, so that this issue goes away. So, my vote is no.

DR. GROSS: Dr. Ringel.

DR. RINGEL: My vote is yes, and the things I would like to have included, first of all, I think there needs to be a loop for the gynecologic consult, and I didn't see that on here.

There should be no return visits solely for picking up lab slips or prescriptions, that someone should--I am not sure it would work again--but check the urine for red blood cells to see if they are menstruating.

Go through the scenario, whatever we choose, for various real world situations like, you

know, patient can't get in because it is snowing, physician is on vacation for a week, it's a college student, they start one place, they end up finishing with another dermatologist in another place, is this going to work.

I think that the pharmacist should check to make sure that there is at least a month between picking up the prescription and having registered. I do think that whatever education we do, there really do need to be pilot studies, and I agree with Dr. Wilkerson, to make sure that when we are educating patients, that we are doing it optimally, otherwise, I don't think it is worth very much.

Finally, I think that we should start to, before patients even begin this, we should start to collect their photos, digital photos of those acne patients. Even if we don't restrict its use, let's find out who it is being used on, and then we can talk about it later.

DR. GROSS: Thank you.

Dr. Vega.

DR. VEGA: I vote yes to the Roche core

proposal with the following modifications. The physician's office should be--the physician should be responsible for entering the pregnancy test into the system, and at the same time, obtain the confirmation number that will be included in the prescription, so that the pharmacy only needs to confirm that authorization number and add the product information to the prescription before dispensing, and to add the voluntary survey, so that we can obtain the information in the 30 days after treatment with Accutane.

DR. GROSS: You want a voluntary or a mandatory survey?

DR. VEGA: They are proposing that the survey, their proposal says it is mandatory?

DR. GROSS: No, I am asking what you are favoring.

DR. VEGA: What is their proposal? I don't see any proposal for a survey.

DR. GROSS: Right, okay.

DR. VEGA: This proposal has no survey. I am saying that there should be a survey, and the

survey to collect patient information should be voluntary.

DR. GROSS: Dr. Day.

DR. DAY: I vote yes for the core program with most of the provisions that have been suggested today, and if some of those don't occur, I would change my vote.

I would like to just say in the patient education side, not only true comprehension testing, but I think some reminder tools can be developed that are very usable and for Art Levin's concern about adding in some other neat little thing that hasn't been tried, there is a huge literature about prospective memory.

Most of memory we think about as what we remember from the past, but prospective memory is remembering to do something in the future, and there are specific tools that can be used to enhance that, so a refrigerator magnet with a little tag you have to take off and write down the start of the period, and take that in for testing, and so on, with reminders continue to use two forms

of contraception or whatever it is.

So, within patient education, attention to prospective memory, as well as true comprehension.

DR. GROSS: Dr. Kibbe.

DR. KIBBE: I am going to vote no. I don't see that this program is going to significantly impact the 1 percent of the women who cannot navigate successfully through this program.

Right now we have 99 percent of the women who use the drug and don't get pregnant, and hence have obtained the correct education, obtained the right outcome. What we don't have, and what we need desperately, is an understanding of why those who made it, made it well, and why those didn't, didn't.

Unless you have that, how can you change a program and expect it to increase its impact if you don't even know what you are trying to change it to do. In that case, if we change this, and we make it more onerous, and it clearly will be more onerous, what is the likelihood?

Well, we have three outcomes. One, things

stay the same. Two, things get better. Three, things get worse. So, if we don't have any data on which we know that this is going to impact the 1 percent that we want to impact, then, how can we say okay, let's change it and see what is going to happen, and lose some of what we are doing well.

You can't argue one way or the other without facts, which one of those three outcomes you are going to get. It is like the forward pass in football, right? Three things can happen, and two of them are bad and one is good.

I think that is what we need. I think that we need to continue to do the educational processes we are doing because it seems to be working, and I don't see that this is a great benefit or improvement over it.

DR. GROSS: Dr. Gardner.

DR. GARDNER: I am concerned about the implication of a no vote for what will happen next, so I guess I concur with Dr. Wilkerson and Dr. Kibbe that when we are trying to move the whole system to improve 1 percent or something on that

order, and don't have the information we need to do it, I think that my inclination would be to leave the current system in place and direct the companies, recommend to the companies that instead they devote the next year to the kinds of failure analyses and other suggestions that have been made here, and perhaps cognitive studies, pilot studies, and come back to us and say here is what we learned, now what changes make sense.

So, that is a long no with caveats.

DR. GROSS: I would just like to remind everybody that we voted unanimously to not continue the current program.

DR. GARDNER: Then, yes with caveats.

DR. KIBBE: Can I remind the Chair that I objected to that vote?

DR. GROSS: That's okay, you abstained.

DR. KIBBE: But I mean that reasoning is because if we don't like this one, we have to have something.

DR. WHITMORE: I think, at least for me--

DR. GROSS: Wait a minute. Let's continue

to go around the table.

So, Jackie, what is your vote?

DR. GARDNER: Yes, with caveats relating to research.

DR. GROSS: Sure, agreed.

DR. KATZ: I think having to vote just on this yes or no limits many people. My vote is no, because I would continue the current program mandating patient enrollment, they are not going to get the drug unless they enroll.

That would satisfy our lack of being able to keep track afterwards, and perhaps have the pharmacist have to get verification of the dates or the actual pregnancy tests, or at least the date, as Dr. Raimer mentioned.

Just two comments. It is not 1 percent, it's 0.1 percent of the population, and the suggestion that nodular cystic acne is some sacred separate entity and everything else is okay, for the folks around the table who are not dermatologists, pustular acne is very severe and very scarring, and what is severe to you may not be

severe to me, and a lot of it depends upon patient-physician interaction, and somebody someplace else evaluating a photograph is the most draconian aspect that I have heard.

They may not think it is severe enough. I see patients who have fairly severe acne affecting their life, and they said they didn't get Accutane because the doctor didn't think it was sufficiently severe. Nothing else has worked, but the doctor didn't say--well, if the doctor's daughter had that problem, maybe they would feel differently.

So, my vote is no, but with modifications to the present program, mandating enrollment and having stricter confirmation of the two pregnancy tests before treatment and pregnancy tests during treatment.

DR. GROSS: Sarah Sellers.

DR. SELLERS: I vote yes. My comments are that I would request for certain elements that have been undefined, that with respect to patient interactions with the registry, that any data that is collected is collected in a manner, so that that

data will be usable for further analysis and potential observational studies.

I also would recommend that the informed consent document be modified to a process that can be evaluated, because as it stands now, it really is a document that asks questions about whether a patient has received a video, but not if the patient has viewed and understood the video.

I would also ask that we explore consequences for noncompliance, and that's it.

DR. GROSS: Thank you all. I know it is tough to put our nickels down, but the Agency is asking us for our opinion, and in the absence of enough evidence, we have expert opinion, and that is why we are all sitting around the table.

The vote is 16 to 8 in favor of accepting the Roche program as a core program for all use of isotretinoin.

Let's take a break and reconvene in 15 minutes and we will try to put together a list for our next round.

[Break.]

DR. GROSS: There were a number of excellent suggestions as we went around the room and took a vote, probably too many suggestions to vote on them individually, so I would like to propose that we lump some of them together.

I am going to make a suggestion on four or five things that might be in our first vote, that I got a sense there might be unanimity to some extent.

The first was that there be a centralized registration system, that all manufacturers use the same registration system. That would be No. 1.

No. 2, that as part of the entry criteria, a digital photo be sent to the central registration system to document the indication for the drug.

The third is that the FDA conduct some research where they try to determine whether or not the patient understands the consent form that they signed and that the patient understands the educational information given them on the drug.

The fourth item is that there be a mandatory survey.

Would anyone like to comment on these things?

MR. LEVIN: I would like to add one other item which I think it has been described in different ways, and that is addressing the lack of data underlying failure, and perhaps that is something that the FDA should be asking the sponsors, and I use the plural, the generics and brand name companies, to be doing, to be conducting a study to look at failures and to try to bring to light why people fail in this program.

DR. GROSS: That goes along with Dr. Crawford's suggestion that FMEA, failure mode and effects analysis, or something like that be conducted in those particular situations. So, we can add that in as a fifth item.

MR. LEVIN: I just want to add, as we saw in S.T.E.P.S., I mean I think one of the things that was somewhat impressive about S.T.E.P.S. is it seems to be recognizing that it should be a work-in-progress. It is learning from experience and it is changing.

One of the changes was that it created six different risk categories that allowed for some interventions and oversight based on those risk categories, and perhaps we should ask for a loop, that as we discover the reasons for failure, that we sort of go back to the program and see how to apply those lessons to this program.

DR. GROSS: Okay. Any other comments?

Yes, Sarah Sellers.

DR. SELLERS: My comments on evaluating the informed consent process were not meant to imply that the FDA do studies. In fact, it's the sponsors' responsibility, not the FDA's, to make sure that the program is effective.

So, I wouldn't support the FDA doing the studies.

DR. GROSS: But you would support that research be done by someone.

DR. SELLERS: By the sponsors, yes, generic and Roche. I think the whole informed consent subject needs to be designed and implemented into the system in a way that allows it

to be evaluated and that makes it a process, not just an informed consent sheet.

DR. GROSS: Any other comments?

Yes, Dr. Epps.

DR. EPPS: I am not in favor of digital photography. Research should be done. I agree that I don't think it's FDA's responsibility to do that although they could certainly advise on it. Surveys, it is okay.

Certainly, I agree we need to find out the failures, the tail is wagging the whole dog, and we need to find out why those people could not accomplish not becoming pregnant from whatever reason, whether it was the doctor, the pharmacy, or their own issue, but I don't think we need to send around digital photos.

DR. GROSS: Dr. Ringel.

DR. RINGEL: I would suggest changing the word on the photo item from documentation to data gathering. I don't want to give the idea that someone is going to be sitting there judging each photo, but I do think that there should be some

documentation of what is being treated, so that we know if there is a problem or not.

DR. EPPS: That is what the medical record is for also.

DR. GROSS: What was the implication, Dr. Epps, that you have a digital photo in your medical records?

DR. EPPS: No. We document physical exam. I don't think we need photographs. I don't think that needs to be central issue or centralized.

DR. GROSS: Dr. Cohen.

DR. COHEN: I just wanted to ask Dr. Ringel where that would be documented.

DR. RINGEL: Whatever central registry.

DR. GROSS: Dr. Whitmore.

DR. WHITMORE: I agree that photographs are not necessary. I would also say that Accutane is used off label for things that are not acne, too, so I am not sure where you would be going with that in those cases.

DR. RINGEL: We could document the acne ones.

DR. GROSS: So, maybe we had better take the photo as a separate item rather than bunching it in.

DR. WILKERSON: With all due respect, I think photographs are the venue of clinical studies, and they are hard enough there with standardized photography, let alone everyone sending in their snapshots, and I think we would end up with a repository of nothing that was of particular clinical usefulness if they are not standardized and done in clinical format.

If the floor is open for motions, which I assume it is, Mr. Chairman?

DR. GROSS: A motion on the other items mentioned?

DR. WILKERSON: Well, any of them. I am assuming we are considering all sorts of items.

DR. GROSS: So, something else you want to add to this list?

DR. WILKERSON: Yes. Being a sore loser, I would like to put a motion forward that the current concepts be studied for cost of

implementation and pilot studies prior to being implemented on the entire country. That is my motion.

DR. WHITMORE: Second.

DR. GROSS: And that would be done by the manufacturers?

DR. WILKERSON: Yes, and I do favor one representative of all the manufacturers.

DR. GROSS: Let me read the list and let's take a vote.

So, the items on the list that we will be voting on. There should be a centralized system for all manufacturers, so any patient, no matter which drug they use, will be registered in a common system.

The second, that research be done to assess the patient's understanding of the consent form and the educational information.

Three, that there be a mandatory survey, and, four, that we do failure mode analysis on women that become pregnant.

The last item is that there be an

assessment of the cost of implementing the program.

DR. COHEN: It's root cause analysis, not failure mode. Failure is prospective, root cause is after it has happened.

DR. GROSS: FMEA is before it happens, you are right, RCA.

Mr. Levin, would you like to register your opinion, yea or nay?

MR. LEVIN: Is it one yea or nay, or is it yea with? It is a very complex package, and up until the last issue where the person proposing that suggestion tied it to I think a delay in moving ahead pending pilots.

DR. GROSS: That was not my impression.

MR. LEVIN: I just want to clarify it.

DR. GROSS: Dr. Wilkerson, is that what you wanted?

DR. WILKERSON: Yes, this does not mean that we discontinue the current system. What it means is that we evaluate going forward before we plunge the entire country into chaos because whenever you change systems, you are going to have

several months of chaos during which time the current system's effectiveness will probably also be degraded.

So, I think before we do that, we want to make sure that the program that we are moving to actually is accomplishing what we think it is going to accomplish, because it is going to add many layers of burden and cost to physicians, pharmacists, and patients.

DR. GROSS: Let's take that off the list then and we can deal with it separately.

So, we have centralized system, registration system for all manufacturers, research as outlined, mandatory survey, and root cause analysis.

MR. LEVIN: Arthur Levin. Yes.

DR. SAWADA: Kathy Sawada. Yes.

DR. VENITZ: Jurgen Venitz. Yes on all four.

DR. BERGFELD: Wilma Bergfeld. Yes, with the exception of the mandatory survey. I am not sure it should be mandatory. I would suggest it be

voluntary.

DR. RAIMER: Sharon Raimer. Yes.

MS. KNUDSON: Paula Knudson. Yes.

DR. BIGBY: Michael Bigby. Yes.

DR. HONEIN: Peggy Honein. Yes, and I prefer mandatory survey, but if that can't be implemented, I would want a voluntary survey rather than nothing.

DR. COHEN: Michael Cohen. Yes.

DR. WHITMORE: Beth Whitmore. As far as the recommendation looking into the cost of doing all this, I would suggest a one-year period where patients are required to have a pregnancy test along with the yellow sticker and assess pregnancy rates during that time prior to initiation of this central program.

DR. GROSS: So, that will have to be a separate consideration.

MS. SHAPIRO: Robyn Shapiro. Yes.

DR. EPPS: Yes, voluntary survey.

DR. GROSS: So, that is yes to everything, but the survey should be voluntary?

DR. EPPS: Yes. I mean I am not in favor--well, I have already said that I am not in favor of registry--but if you are going to have a registry, everybody should use the same thing.

DR. SCHMIDT: Yes to all.

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. GROSS: Peter Gross. Yes to all.

DR. WILKERSON: Michael Wilkerson. Yes. The survey should be voluntary, though.

DR. RINGEL: Eileen Ringel. Yes to all.

DR. VEGA: Amarilys Vega. Yes, but that the survey should be voluntary.

DR. DAY: Ruth Day. Yes to all.

DR. KIBBE: Arthur Kibbe. Yes.

DR. GARDNER: Jackie Gardner. Yes.

DR. KATZ: Robert Katz. Yes.

DR. SELLERS: Sarah Sellers. Yes.

DR. GROSS: The way I read the vote is it was unanimous yes with a caveat that the mandatory survey, there were 5 people who requested it be voluntary, and the rest agreed to mandatory. So, that would be 19 agreed to mandatory.

I think we are accomplishing a lot here. The other items we may have to take up individually.

Dr. Wilkerson, do you want to vote on delaying the whole thing until a cost analysis is done, or do you want to withdraw that? I am just trying to be fair.

DR. WILKERSON: Samuel Clemens once said that--I will paraphrase--you don't want to watch sausage or a law being made. I really think we need some regional studies to see if these programs really work. I really do have concerns about transition periods going between different methodologies for trying to accomplish what we all want to accomplish here.

I just don't want to complicate this and not see any--because it is going to be another three years before we see something. We should have been doing pilot studies the entire time to find out what really works, and then try to apply those to the populace in general.

So, my motion stands to delay pending

pilot studies and financial impact of these recommendations.

DR. GROSS: Is there a second to the motion?

DR. WHITMORE: I would like to second that.

DR. SCHMIDT: I second it.

DR. GROSS: That was quick. I would like to just make a comment. Having done some cost effectiveness/cost benefit analyses where you come up against the issue of at least when it comes to mortality, the value of human life used to be 50,000, now it is 200,000. That is accepted in the literature.

The value of quality of life, I am not familiar with what those financial numbers are, but anybody here familiar with--I guess it depends on what aspect of quality of life you are talking about.

DR. WHITMORE: I am not sure.

DR. SELLERS: I am sorry, I was just going to say it will become very difficult because again

we don't have the data that we need to fully define the scope of the problem. We have reported data. We don't know the entire scope of patients who are affected by this drug to do a cost-benefit analysis.

DR. GROSS: Somehow we are going to need that kind of information to do it, because how are we going to say that this program is worthwhile doing or not doing.

DR. SELLERS: Well, it's worthwhile, in my mind, because we are going to be collecting data through the registry, and that will allow us to start making better estimates of rates and persons who are affected.

DR. GROSS: We have a motion on the table to delay implementation of the study until--

DR. WHITMORE: Could I just say that our goal is to reduce pregnancies, and if during that period before implementation of this, when we are taking a pregnancy test to the pharmacy, that is required with the woman to have the prescription filled, if we can reduce pregnancy rates during

that time, I think you can assess how much you are reducing rates of pregnancy with that.

You are not going to come up with a cost-benefit analysis of this program, because you are not going to know how much it is going to reduce pregnancy. In the meantime, you could at least be studying how much just implementation of a pregnancy test going along with the woman reduces the rate or pregnancy that is occurring right now.

DR. GROSS: Dr. Crawford.

DR. CRAWFORD: Just to state I will be voting against this because in terms of the FDA's mandate, looking at safety and efficacy, I don't think a cost effectiveness analysis is appropriate beyond perhaps quality of life issues, and I do know for a fact that while I do think sometimes economic analyses are very well done, I am aware of how without very proper sensitivity analyses and consideration of a variety of variables, those numbers can be biased. So, I will be voting against this.

DR. WHITMORE: I wonder if Dr. Wilkerson

was talking more about just the cost as opposed to cost-benefit, because we are not going to be able to measure benefit, the question is cost.

DR. WILKERSON: Mine was more the cost of implementation to physicians, their office, to health care plans, not the cost of life or any of those sort of things, so no, it is not a cost-benefit, it is a cost of implementation, the extra 10 or 15 minutes that it takes every doctor or nurse to punch in all this data, and in the end, you know, the question at the end of the day, we all feel better when we have done something, but if that work does not actually produce an end product, then, what is the point of having done that extra work, and that is a critical question here.

DR. GROSS: The other critical part of it is the production of a deformed child, there certainly is a cost associated with society taking care of that child as far as the anguish of the child and the family.

DR. WILKERSON: Oh, absolutely, but if the end result of tightening this up means that we have

the paradoxical effect of seeing more deformed children, then, what is the point of that? We don't know the answers.

MR. LEVIN: Again, I would like to emphasize this is modeled on programs about which we have some evidence.

DR. WILKERSON: But we only have 4- or 5,000 women.

MR. LEVIN: I understand that.

DR. WILKERSON: It's totally different populations.

MR. LEVIN: I mean it's the best evidence we have, and to hypothesize that somehow it is dangerous to proceed based on that evidence, I don't know, I think it's a disservice to the people who are being hurt and will be hurt, and we saw dramatic testimony today about what the cost of not doing this thing correctly.

DR. WILKERSON: Then, why haven't we been worried about that for the last 22 years?

MR. LEVIN: I couldn't agree with you more.

DR. WILKERSON: This is not a new problem.

DR. GROSS: Hold on a minute. Can we get some clarification from the FDA? Dr. Kweder?

DR. KWEDER: I am not sure what the question is. What would you like me to clarify?

DR. GROSS: I just thought you had a comment.

DR. KWEDER: No.

DR. GROSS: Basically, this motion is to delay implementation of the program that we approved by a two-thirds majority, delay it until a cost analysis is done that would basically undo everything we have done so far.

Mr. Levin.

MR. LEVIN: Arthur Levin. No.

DR. SAWADA: Kathy Sawada. No.

DR. VENITZ: Jurgen Venitz. Before I announce my vote, I just want to point out the main reason why I voted in favor of the core proposal, and the amendments that we just passed, so we can generate data, because there will be another committee meeting in 5, 10 years, and they are

going to ask the same questions that were asked 4 years ago and 10 years ago, and there were no data to support any contention whether the current system works, it doesn't work, how many people are at risk, are we talking about 1 percent or 0.1 percent.

So, the reason why I am voting against the motion, meaning not to delay, is because I want for something to be in place, that allows us to gather the data, so the next committee that is going to review this will have an evidence database to base their decision on.

DR. BERGFELD: Wilma Bergfeld. I am in a great dilemma because what I would have liked to have heard was that we were going to have it move forward, and we would pilot the program before we launched it, with or without a financial note to that.

DR. WILKERSON: That is the intention, is to do pilot studies as we move forward.

DR. BERGFELD: Not to hold up the program, but to move forward, but before launching, to

pilot--

DR. WILKERSON: In a pilot sense, not as an entire rollout to the entire country.

DR. BERGFELD: If that was the intent, I would vote to do this as a pilot. I am not sure if that is a yes or no.

DR. GROSS: Dr. Wilkerson, let me clarify it for the group. You are saying that there be some kind of a pilot study with a cost assessment?

DR. WILKERSON: I think that was what I originally said.

DR. GROSS: I didn't hear that, but that is fine.

So, we have 3 nays and 1 yea.

Dr. Raimer.

DR. RAIMER: Sharon Raimer. I am voting for a pilot program. I think the S.T.E.P.S. program as it has been used in Thalidomide, I don't think we can cross it over to our population, because those women were mostly in their 40s, and they were critically ill, most of them, or seriously ill, they had malignancies, so a young,

healthy population, just because it worked in an older, sick population doesn't mean it is going to necessarily work in ours, so I think we need to see some pilot studies to see if it does work and get the thing going, how feasible it is.

DR. GROSS: Dr. Knudson.

MS. KNUDSON: Yes, because it will be a pilot study to determine if it's feasible and what the cost might be.

DR. BIGBY: Michael Bigby. No.

DR. HONEIN: Peggy Honein. No.

DR. COHEN: Michael Cohen. No.

DR. WHITMORE: Beth Whitmore. Yes.

MS. SHAPIRO: I have a question. I am not quite sure what we are voting on. We would do a pilot study, not only to look at cost, but also effectiveness, right? Okay.

And in the rest of the country, where the pilots were not going on, despite our earlier vote, they would be status quo, is that right?

DR. GROSS: The effectiveness, again, this is another concept introduced, effectiveness was

not mentioned originally, it was just cost.

MS. SHAPIRO: I would like to ask Dr. Wilkerson then, the person who made the motion, whether or not his intent was to also gather data about numbers of pregnancies.

DR. WILKERSON: Yes. The purpose of this is to determine if doing this act actually results in obtaining the end product that we are looking for, which is namely reduction of pregnancy risk.

MS. SHAPIRO: Which makes sense.

DR. GROSS: Wait a minute. Wait a minute.

If the assessment is effectiveness, then, we would need to know how many people have to be involved in the study to assess effectiveness. Does anybody know that answer?

DR. WILKERSON: It depends on the power of the study.

DR. VENITZ: The current system, you have a voluntary reporting system. That means you are going to generate the same data, just in a smaller scale with a slightly different system.

You still do not know what the pregnancy

rates are, you still cannot interpret any of the numbers other than how many people actually are enrolled in your program.

DR. WILKERSON: But you know what the optimal effectiveness of the intervention that you are trying to do is in a study.

DR. VENITZ: What are you comparing it to?

DR. WILKERSON: That is what you are doing, you are doing a controlled study to know what the optimal effectiveness of your intervention is.

DR. VENITZ: The only thing as far as I understood your motion is, you can assess whether it is feasible to do what the core proposed plan proposes to do, but you cannot assess its effectiveness.

DR. GROSS: We have got a problem here because we have a shifting motion. We started out saying the whole program was going to be delayed until there is a cost assessment. Then, it was changed that there will be a pilot program. Then, it was changed that there was going to be an

assessment of efficacy without any understanding of what the numbers were, what the power requirements were.

Basically, the intent is that the overall program will be delayed. I think that has to be understood.

DR. KWEDER: Maybe I can clarify a little bit from our standpoint. First, I think from our perspective, even though we asked it as a question, doing nothing and making no change is really not an acceptable course of action in our opinion.

I do think if changes are to be made to the system, they need to be made quickly. I don't think this is the kind of thing where we feel that the Agency is in a position to pontificate for long periods of time about what changes should be made, could be made.

So, from that standpoint, your advice today has been very helpful. As regards pilot programs, we would like to hear your ideas about, and you have been offering about, what would constitute a pilot program.

Often what we do is we work with sponsors to develop testing and pilot testing of components of a program rather than an entire program, because we learn a lot about the individual components one at a time, or several in combination.

But we do get into the question of how much of a pilot test is enough and what is it that we are measuring. As you will see further on in some of the questions, we do have a question for the committee about what should be the goal and how do we establish a goal for success and effectiveness.

That is something that we would like to hear from you on whether you are referring to a pilot program or to the entire program.

As regards the issue of cost, we do not, under our statute and regulations, have any authority to regulate medicines or costs of medicines or even particularly costs of programs.

Cost plays out in a different way in how drugs are regulated. Sometimes if things become too expensive, companies make the decision that

they can't participate in such a program, so they will no longer manufacture the product.

That is not a desirable outcome, but in looking at cost-benefit of how much this program costs, it really all comes down to the effectiveness of the program, what is it that we are trying to achieve with the program, and is the program helping us to reach those goals.

We are open to looking at programs that are costly, and we do this all the time, to assess are all of the components of this program necessary, is the investment in every one of these steps or pieces of it really helping us achieve the goal.

That is the kind of question that can be best be addressed by continuous analysis of the program itself, which is something that we have not had a great deal of information on in the programs we have reviewed to date.

DR. GROSS: Robyn, your opinion or your vote?

MS. SHAPIRO: I still don't know what the

motion is.

DR. GROSS: The original motion was that the program be delayed until an assessment of cost be made. That was the original motion.

MS. SHAPIRO: And has it been amended or not?

DR. WILKERSON: Yes, it has. Basically, it is do we proceed with pilot programs or do we proceed with the complete implementation of the program not knowing what the ultimate outcome of it is going to be.

DR. GROSS: But a pilot program, what is a pilot program? How many people are you talking about?

DR. WILKERSON: That's, you know, I mean McDonald's rolls out sandwiches in one part of the country to see if they sell before they take it all over the place.

The same thing here, we are talking about millions and millions of dollars potentially being spent to roll out a program like this, and not knowing if it's going to even produce the end

result that we are looking for.

DR. GROSS: The people who are spending the millions are the ones that suggested the program.

MR. LEVIN: That's right, the sponsor is the one who is bearing that cost.

DR. WILKERSON: Sponsors, patients, physicians, health care delivery systems, insurance companies, we all bear the cost of these programs.

MS. SHAPIRO: I have a question for the Agency.

DR. GROSS: Robin, yea or nay, and let's move on.

MS. SHAPIRO: Can I just ask one clarifying question of the Agency, and then I guess I will abstain, because I still don't know what the question is.

If the motion were to delay rollout of whatever it is we think should be rolled out, pending a pilot program that could, after input from biostatisticians or whomever tell us what the power has to be, you know, what it has to be to

both gather effectiveness data in terms of numbers of pregnancies and gather costs, if we could get all that, and implement that, and in the meantime put the current--maintain the status quo, is that something that the Agency would accept?

DR. KWEDER: I think we would certainly take that counsel under advisement.

MS. SHAPIRO: Okay. That is what I want to vote for.

DR. GROSS: Next, Dr. Epps.

DR. EPPS: I can be in favor of a pilot or trial. Of course the endpoint would be no one starting Accutane who is pregnant, and no one becoming pregnant on Accutane. That would be a more desirable endpoint.

I do think that as it has come down the line, the proposal has evolved, so it is kind of hard to know exactly what the--I know what the intent was, it has evolved, and certainly the 3(b), which was modify the current program with additional risk management tools to reduce fetal exposure, was the FDA's question.

DR. SCHMIDT: I vote for the Shapiro clarification of the motion.

DR. GROSS: What is the Shapiro clarification?

DR. SCHMIDT: That if we could get a pilot program on this motion without slowing down the original process of implementing this, and we can figure out--what I am really concerned about is this is going to be really majorly expensive and a lot of people don't have insurance, and when you start socking people for 600, $2,000, $3,000 a month for medication, even when they pay their co-pays, people who need this stuff are not going to be able to afford it.

That is what I am concerned about. That is why I want a pilot program.

DR. GROSS: Roche said they would provide payment for people who can't afford it.

MR. LEVIN: Peter, could I just say--I hate to be saying the same thing over and over again--we have a program which has costs that this is very similar to, and while it is a different

population, we certainly can get cost information about that program, so we don't have to reinvent the wheel here.

There is a S.T.E.P.S. program out there, there is another program out there dealing with restricted access and restricted dispensing, and I think, you know, we can avail ourselves of the experience from those programs to get from those manufacturers and sponsors what the cost is, so we don't have to go out and pilot this as if we don't have any way to get that information. It makes no sense.

DR. SCHMIDT: Hoffmann-La Roche is out of the business of giving away free Accutane. As far as in Houston, Texas, their rep has been terminated and is with another company, and with the generic companies, you try to get free medicine for people, they have to have their tax returns for the past three years and have to be eating beans and living on the street before they will get free medicine.

So, I would really like to find out where we are going to get all this free medicine and who

is going to pay for it.

DR. GROSS: So, your vote is yes, right? Okay.

Dr. Crawford.

DR. CRAWFORD: Stephanie Crawford. My vote is no delay beyond a reasonable transition period.

DR. GROSS: Peter Gross. My vote is an emphatic no.

DR. WILKERSON: Michael Wilkerson. Yes.

DR. RINGEL: Eileen Ringel. No.

DR. VEGA: Amarilys Vega. No.

DR. DAY: Ruth Day. It has been 22 years. No.

DR. KIBBE: Just a small encouraging comment for the members of the committee. The Agency doesn't have to do anything we tell them to do. So, you guys can vote all the time, any way you want, and they are going to eventually take the sum of the discussion and do what they think is the best for the general public, and the fact that 8 of us are on one side of a vote, and 16 on the other,

might weigh a little bit on it, but also the quality of the argument.

My argument is that we have a system in place today which more than 99 percent of the women who go through the treatment come away without a problem in pregnancy. We have yet to actually figure out why the others fail.

Then, we are going to go to a more complex system. Whenever you go to a more complex system, people don't adhere to it as well as a simpler system. So, we put a more complex system in, we might very well lose ground rather than gain ground.

Now, my colleague said this is a cost-benefit. For me, it is really I want to know whether we are going to gain ground on the numbers or percent of those who aren't pregnant after going through the course of treatment.

If there is a way for someone to pilot it in, to show us that, we are better off than jumping in with both feet and losing if just for the horrible thought of going from 94 to 150 or 180

next year because of the confusion of putting the program in.

Now, that's my concern and that is why I am voting. I think I am voting yes, I am not sure.

DR. GROSS: I gathered.

Jackie.

DR. GARDNER: Jackie Gardner. No.

DR. KATZ: Robert Katz. Away from the table, in the hallway, we are all concerned about cost, but I have been told before around this table, cost is not our concern, and getting involved in this and obfuscating renders our two days here ineffectual.

So, whatever we decide, we should go ahead. An emphatic no.

DR. SELLERS: Sarah Sellers. No.

DR. GROSS: Dr. Shapiro, you voted yes?

MS. SHAPIRO: Yes, with my revisions, right.

DR. GROSS: The nays have it 14 to 8.

As far as the other suggestions are concerned, I don't know that we are going to be

able to reach consensus on it, and maybe what we should do, as Dr. Kibbe pointed out, is make other suggestions that might be considered, and Hoffmann-La Roche and the generic manufacturers will hear them, the FDA will hear them, and maybe we can leave it at that, unless somebody here has a burning issue they want to go through another vote on.

The suggestions that we have heard is recertification of physicians. There was a question on the video. Was that Dr. Bigby, did you comment on that, or who commented on the video?

DR. WHITMORE: I did. It's an excellent video, and I would recommend that all patients view it.

DR. GROSS: The surveillance that is done, the survey that is done should include tracking women who get pregnant.

DR. WHITMORE: I have a question about physician reporting and making that mandatory.

DR. GROSS: Physician reporting. What do you mean?

DR. WHITMORE: Of pregnancies.

DR. GROSS: Where is that in the program?

DR. WHITMORE: I don't know. I think it should be included.

DR. GROSS: Oh, you think it should be included.

DR. WHITMORE: Right.

DR. GROSS: Good. All right. Any other suggestions?

Dr. Cohen.

DR. COHEN: We had the suggestion before about the indication being in the registry, an attestation of the indication.

DR. GROSS: Attestation of the entry criteria, indication for the treatment. Good.

If there is nothing else, I think Question 4 was taken care of by adopting the program because that includes a registry for patients, physicians, and pharmacies, not pharmacists. Anybody want to change that or comment on that?

Ruth.

DR. DAY: I would like the pharmacists

here to convince me it should not be pharmacists. I know it is a lot more work, et cetera, et cetera, but why not?

DR. GROSS: Sarah Sellers.

DR. SELLERS: I agree it should be pharmacists consistent with the type of certification we have for disease management specialists, I think this could be achieved.

DR. GROSS: Dr. Cohen.

DR. COHEN: I was going to say the same thing. I think if anything, it might add to the pharmacists wanting to follow through and comply with the program, et cetera, so go along with it.

DR. KIBBE: There is only one small drawback. I agree that we ought to register the pharmacists, the actual health professional who is responsible for doing it.

The drawback is that if the patient comes to the same pharmacy where multiple pharmacists work, if not all of them are registered, they might run into a problem with the delivery of the prescription or the delivery of the medication

might be delayed until a registered pharmacist, one that is registered with the program as opposed with the state might be there to handle that.

That is a logistics problem.

DR. GROSS: Sarah Sellers.

DR. SELLERS: That is where we have seen noncompliance with the S.T.E.P.S. program. So, that argues for a pharmacist being registered actually.

DR. GROSS: That's it. We seem to have fair unanimity on that. Maybe we had better vote on it because that modifies the Roche program.

Nobody wants to vote?

DR. CRAWFORD: No, but may I make a comment? Certainly, anytime there is any opportunity for professional development with the pharmacists, I am in favor of it although right now, at this point, I think I would be more in favor of registration of the pharmacies.

In the practice of pharmacy in the absence of state laws and regulations, the state board actually looks at institutional policies and

procedures, so unless the pharmacy, in this case, for example, the corporate chains, the independent, whoever owns that community pharmacy, unless they say to do it, it may not be done.

I am concerned, I don't know how many practicing community pharmacies, there are approximately 200,000 pharmacists in the United States, my guess would be perhaps about 70 percent practice in community.

I think it would be very difficult in terms of access, so saying that the pharmacists have to be registered for this particular--certified, whatever the term is for this particular program--it is okay as long as it is realized there will be much less access, much less for the patients.

DR. GROSS: What happens in the S.T.E.P.S. program, is it pharmacists or pharmacies?

DR. SELLERS: Pharmacies. The S.T.E.P.S. program uses pharmacies. We are aware that in pharmacy practice, there are people who are working part time or doing shift work and that some of the

lapses that have been described may, in fact, reflect that the SOPs for the pharmacy aren't perfectly communicated to the individuals who are working there on a part-time basis.

DR. GROSS: Brian.

DR. STROM: To me, it makes no more sense to certify pharmacies than it does to certify physician practices as opposed to physicians. The point is the individual clinician is the one who is going to be doing the care. If the net impact is there are fewer people able to do it, so be it, but that is the same thing as saying certify dermatologists as opposed to dermatology practices. They are the ones making the decisions.

My guess is what will happen would be a move toward what I was looking for before in terms of specialty pharmacies. There will be some pharmacies that will say we need to have all of our pharmacists certified, and there will be some that will say we are not going to do this.

DR. GROSS: Dr. Bergfeld.

DR. BERGFELD: I would concur with that

wholeheartedly. Why would you have two different standards for two different professional groups.

DR. WHITMORE: This brings up an issue about nurse practitioners and PAs.

DR. BERGFELD: What is that issue?

DR. WHITMORE: If they need to be certified or actually if they can be certified and get stickers, and I don't know if they can get stickers or not.

DR. GROSS: Well, certainly the PA that presented, PAs do it under physician license in many states--

DR. WHITMORE: It that under the physicians' certification, though? I imagine it is under the yellow sticker--

DR. GROSS: Not necessarily.

DR. WHITMORE: So, they should go through some kind of training.

DR. GROSS: That makes sense and nurse practitioners can in many states write prescriptions independent of physicians.

Stephanie.

DR. CRAWFORD: Thank you. Real quickly with that one, I do believe anyone with prescriptive authority should be the same rules. I am not at all opposed to the pharmacists being certified. I welcome it. It is just I am saying if it is done, we need to realize that it is limiting access and also, Dr. Strom, when it says, I presume, when it says the pharmacy is certified, that means the pharmacist in charge, who also he or she informs all of the pharmacists who work there, be they part time, full time, registry, whatever the case may be, what the policies are for that pharmacy.

DR. GROSS: Maybe we had better vote on this. I guess the question would be that all prescribing health care providers should be registered in the program, so that would include physicians, pharmacists, PAs, and nurse practitioners.

MR. LEVIN: Arthur Levin. Yes.

DR. GARDNER: Point of order. Not all pharmacists prescribe.

DR. GROSS: Health care providers. I am sorry. Pharmacists, as well as all of those who prescribe, meaning PAs, nurse practitioners, and physicians. I am sorry I didn't state it clearer.

DR. SAWADA: Kathy Sawada. Yes.

DR. VENITZ: Jurgen Venitz. Yes.

DR. STROM: Brian Strom. Yes.

DR. BERGFELD: Wilma Bergfeld. Yes.

DR. RAIMER: Sharon Raimer. Yes.

MS. KNUDSON: Paula Knudson. Yes.

DR. BIGBY: Michael Bigby. Yes.

DR. HONEIN: Peggy Honein. Yes.

DR. COHEN: Michael Cohen. Yes.

DR. WHITMORE: Beth Whitmore. Yes.

MS. SHAPIRO: Robyn Shapiro. Yes.

DR. EPPS: Roselyn Epps. Yes.

DR. SCHMIDT: Jimmy Schmidt. Yes.

DR. CRAWFORD: Stephanie Crawford. Yes.

DR. GROSS: Peter Gross. Yes.

DR. WILKERSON: Michael Wilkerson. Yes.

DR. RINGEL: Eileen Ringel. Yes.

DR. VEGA: Amarilys Vega. Yes.

DR. DAY: Ruth Day. Yes.

DR. KIBBE: Arthur Kibbe. Yes.

DR. GARDNER: Jackie Gardner. Yes.

DR. KATZ: Robert Katz. Yes.

DR. SELLERS: Sarah Sellers. Yes.

DR. GROSS: Well, what a nice way to end up.

The last question, Question 5. Please identify the critical benchmarks for determining the success or failure, for example, reducing to zero the number of women who are pregnant at the initiation of isotretinoin treatment.

Does anybody have any other suggestions for the FDA as to benchmarks for assessing success or failure?

Ruth.

DR. DAY: Excuse me. We never did vote on the other things that came up in the other category. They were originally the recertification, the video, the survey, the indications and the registry, the pharmacists, and then it all went into what we voted, was all health

care providers. So, what happened to those other items?

DR. GROSS: The other items were suggestions to the FDA and the manufacturers to consider. We weren't going to vote on it.

Dr. Ringel.

DR. RINGEL: Because achieving an endpoint of zero pregnancies is simply not reasonable even though it's what we are all striving for, I suggest that we accept as an endpoint continuous quality improvement, that each time, each year, each time this program is assessed and the change has been made, it should be better than the last time.

DR. GROSS: Excellent suggestion. So, there should be successive iterations of quality improvement as data gets fed into the system.

DR. WHITMORE: I would say a good goal would be to reduce to zero the number of women who have a positive pregnancy test at the initiation of therapy.

DR. GROSS: Anything else?

DR. STROM: Do you know what the

benchmarks are for the S.T.E.P.S. program?

DR. GROSS: Anybody from the FDA or elsewhere who want to comment on that?

DR. TRONTELL: I will invite anyone to speak. I don't believe, in fact, in any of these areas we have set an absolute threshold or ceiling for performance, that it has been a matter of continued re-evaluation.

DR. GROSS: Maybe we could state it as goals, goals, as well as benchmarks.

DR. SELIGMAN: We already have goals, I think.

DR. GROSS: Right. Sorry.

MS. SHAPIRO: I just have a question about the last suggestion. Doing better, does that mean in terms of absolute numbers or rates?

DR. WILKERSON: We don't know what the rates are.

MS. SHAPIRO: Right. That's a problem.

DR. GROSS: Dr. Bigby.

DR. BIGBY: Actually, I think that is a very important question, and I think that we should

actually look at absolute numbers. I mean if the rate falls and the uses goes up and the number of deformed children goes up, and exposures goes up, nobody is going to be happy with that, so I think you have to look at the absolute numbers.

DR. RINGEL: As the person who made the proposal, I definitely agree with that.

DR. WHITMORE: Can I remind us that all we are doing is targeting the initiation of Accutane in a pregnant woman, so we are affecting that 12 percent, and nothing else, unless education actually works.

DR. GROSS: Dr. Vega.

DR. VEGA: We need to be aware that once we have global registration and we start capturing a larger population, we might end up seeing a larger number of pregnancies that were slipping down the cracks, and when we capture that population, the numbers will go up, and if set that goal, we will be calling that a failure, when, in fact, we are starting to see the real picture.

DR. GROSS: A good point.

Dr. Bigby.

DR. BIGBY: Can I put that slide up? The one thing outside of detecting this group of women who are pregnant when they start the medicine, and eliminating them because we do pregnancy tests, two pregnancy tests before initiating treatment, is that we really need to look at how well sort of contraceptives work and what we are actually doing to change the number of women who get pregnant.

DR. UHL: People want to see this one as well. There are two separate slides that we have prepared.

[Slide.]

This one is the percentage of women experiencing unintended pregnancy during the first year of perfect use of multiple different contraceptive products. These are data from the Contraceptive Technology Reference in 1998.

[Slide.]

I am happy to go back and forth between these. This slide are contraceptive failure rates. As you can see, both of these are rates calculated

in a different way, a different manner. These are contraceptive failures. These are rates per 1,000, I believe there were 1,000 women. Peggy Honein may be able to comment even better.

I take this back. I thought these were CDC data. These are ACOG data. The only one that is not per 1,000 is for the IUD data, which are cumulative 5-year failure rates. I think it is 1,000 women years.

DR. KATZ: Excuse me. The tubal ligation, does that mean 7.5 to 36 per 1,000 failure?

DR. UHL: That is total contraceptive, yes. If you look at the previous slide, that is why there is two separate slides here. This is unintended pregnancy with within the 12 months following the initiation of that method. So, here you have a tubal ligation failure rate of 0.5 percent. But these are two separate sources of data.

These also are per one contraceptive method as Dr. Kweder alluded to this morning. We don't have data on failure rates using two sources

of contraception.

Maybe patients need to be educated with this information.

DR. EPPS: Are all intrauterine or some of them ectopic pregnancies?

DR. UHL: I don't have that data.

DR. GROSS: I think we are kind of winding down here. Are there any other points? Yes, Dr. Ringel.

DR. RINGEL: I think there is two points. The first is that even though the IUD looks very good, people who are not physicians need to know that it carries a significant risk of sterility and pelvic infections, and most gynecologists would refuse to implant an IUD, for example, in a 16-year-old girl, so unfortunately, that is not a possibility.

Another thing to look at is, in fact, oral contraceptives that so many women use and really in use have a fairly high failure rate. I hate to harp on it again, but anything we can do as an education--I forgot what you called it--something

to prospectively remind people to take that pill or remind them if they haven't taken a pill.

I don't care if you want to make a box or if you want to make a magnet or a sticker or anything that you could devise to help that number would probably go a long way.

DR. GROSS: If there are no other comments, I would declare the meeting adjourned. I want to thank the Advisory Committee for their incredibly excellent input. I appreciate the audience's contributions.

Once again, thank you all for an excellent two days.

[Whereupon, at 3:45 p.m. the hearing was adjourned.]

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