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

Thursday, February 26, 2004

8:00 a.m.

Hilton Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland 20877

PARTICIPANTS

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE:

Peter A. Gross M.D., Chairman
Shalini Jain, PA-C, M.B.A., Executive Secretary

Michael R. Cohen, R.Ph., M.S., D.Sc.
Stephanie Y. Crawford, Ph.D., M.P.H.
Ruth S. Day, Ph.D.
Jacqueline S. Gardner, Ph.D., M.P.H.
Arthur A. Levin, M.P.H.
Robyn S. Shapiro, J.D.
Brian L. Strom, M.D., M.P.H.

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE:

Roselyn E. Epps, M.D.
Robert Katz, M.D.
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Sharon S. Raimer, M.D.
Eileen W. Ringel, M.D.
Kathleen Y. Sawada, M.D.
Jimmy D. Schmidt, M.D.
Elizabeth S. Whitmore, M.D.
Michael G. Wilkerson, M.D.

CONSULTANTS (Voting):

Wilma F. Bergfeld, M.D.
Michael E. Bigby, M.D.
Margaret Honein, Ph.D., M.P.H.
Arthur H. Kibbe, Ph.D.
Sarah Sellers, Pharm.D.
Amarilys Vega, M.D., Ph.D.
Jurgen Venitz, M.D., Ph.D.

GUEST SPEAKER (Non-Voting):

Richard K. Miller, Ph.D.

PARTICIPANTS (Continued)

FDA STAFF:

Jonca Bull, M.D.
Steven Galson, M.D., M.P.H.
John Jenkins, M.D.
Sandra Kweder, M.D.
Paul Seligman, M.D., M.P.H.
Anne Trontell, M.D., M.P.H.
Jonathan Wilkin, M.D.

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. GROSS: Good morning. I am Dr. Peter Gross. I am Chair of the Drug Safety and Risk Management Advisory Committee. I would like to thank you all for coming this morning, and the first order of business is for us to go around the room and introduce everybody at the table. So, I am Dr. Peter Gross. I am Chair of the Department of Internal Medicine at Hackensack University Medical Center and New Jersey Medical School.

MS. JAIN: Shalini Jain, Executive Secretary, FDA, Center for Drug Evaluation and Research.

DR. WILKERSON: Michael Wilkerson, MD., private practice, Tulsa, Oklahoma.

DR. RINGEL: Eileen Ringel, I am in private practice in Waterville, Maine.

DR. DAY: Ruth Day, I direct the Medical Cognition Laboratory at Duke University and I am on the Drug Safety and Risk Management Committee.

DR. KIBBE: Art Kibbe, Chairman of the

Pharmaceutical Sciences Department, Wilkes University School of Pharmacy and Chairman of the Pharmaceutical Sciences Advisory Committee to the FDA.

DR. GARDNER: Jackie Gardner, Professor of Pharmacy, University of Washington, and Drug Safety and Risk Management Advisory Committee.

DR. KATZ: Robert Katz, I am in private practice in Rockville, Maryland, and Clinical Assistant Professor of Dermatology at Georgetown University.

DR. SELLERS: Sarah Sellers, Pharm.D. I am a Masters in Public Health Candidate at Bloomberg School of Public Health.

DR. TRONTELL: Anne Trontell, Deputy Director of the Office of Drug Safety in the FDA Center for Drugs.

DR. SELIGMAN: Paul Seligman, Director of the Office of Pharmacoepidemiology and Statistical Science, also in the Center for Drugs at the FDA.

DR. WILKIN: Jonathan Wilkin, Director of the Division of Dermatologic and Dental Drug

Products in CDER, FDA.

DR. BULL: Good morning. Jonca Bull, Director, Office of Drug Evaluation V in the Office of New Drugs, Center for Drug Evaluation and Research.

DR. KWEDER: Sandra Kweder, Deputy Director of Office of New Drugs in CDER.

DR. GALSON: Steve Galson, I am the Acting Director of the Center for Drug Evaluation and Research.

MR. LEVIN: Art Levin, I am the consumer representative on the Drug Safety Committee.

DR. SAWADA: Kathleen Sawada, dermatologist, private practice in Lakewood, Colorado.

DR. VENITZ: Jurgen Venitz, Associate Professor, Virginia Commonwealth University and Chair of the Clinical Pharmacology Subcommittee.

DR. STROM: Brian Strom, I am Chair of the Department of Biostatistics and Epidemiology at the University of Pennsylvania School of Medicine, and I am a member of the Drug Safety and Risk

Management Committee.

DR. BERGFELD: I am Wilma Bergfeld, dermatologist and dermatopathologist, head of Clinical Research Department of Dermatology at the Cleveland Clinic.

DR. RAIMER: Sharon Raimer, Chairman of Dermatology at the University of Texas in Galveston.

MS. KNUDSON: Paula Knudson, I am the IRB administrator for the University of Texas at Houston, and I am with the Dermatology Advisory Committee.

DR. BIGBY: I am Michael Bigby. I am a dermatologist at Beth Israel Deaconess Medical Center and Harvard Medical School.

DR. HONEIN: I am Peggy Honein. I am an epidemiologist with the Birth Defects Center at the Centers for Disease Control and Prevention.

DR. COHEN: Mike Cohen, I am a pharmacist with the Institute for Safe Medication Practices, and I am with the Drug Safety and Risk Management Advisory Committee.

DR. WHITMORE: Beth Whitmore, I am in private practice in Wheaton, Illinois.

DR. SHAPIRO: Robyn Shapiro, I am Professor and Director of the Center for the Study of Bioethics at the Medical College of Wisconsin, and I am on the Drug Safety and Risk Management Advisory Committee.

DR. EPPS: Roselyn Epps, Chief of the Division of Dermatology in Children's National Medical Center, and also a member of the Dermatologic and Ophthalmic Drugs Advisory Committee.

DR. SCHMIDT: I am Jimmy Schmidt, in clinical practice from Houston, Texas and I am on the clinical faculty of University of Texas and Baylor Medical School.

DR. CRAWFORD: Good morning. Stephanie Crawford, Associate Professor, University of Illinois at Chicago College of Pharmacy, and I am a member of the Drug Safety and Risk Management Advisory Committee.

DR. GROSS: Thank you all, and now I would

like to ask Shalini Jain to read the conflict of interest statement.

Conflict of Interest Statement

MS. JAIN: The following statement 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 discussions.

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 maybe obtained by submitting a request to the Food and Drug Administration's Office of Management Programs, Division of Freedom of Information, HF1-35 5600 Fishers Lane, 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 may apply to each member, consultant and guest speaker. In addition, there will be no industry representatives at today's meeting. As you may be aware, the Food and Drug Administration has appointed industry representatives that currently serve on each of these committees but Annette Stemhagen, Dr.PH., the industry representative to the Drug Safety and Risk Management Committee, and Peter Kresel, M.B.A., the industry representative to the Dermatologic and Ophthalmic Drugs Advisory Committee, work with sponsors that are directly impacted by the matters

before the committee. FDA has contacted three industry representatives from other Center for Drug Evaluation and Research committees that have experience with risk management issues and with FDA advisory committee processes. 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. Louis Morris, a member of the Drug Safety and Risk Management 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 the issues at hand outside the advisory committee meeting. In the event that the discussions involve any other products or firms not already on the agenda for which FDA participants have a financial interest, the participant's 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 wish to comment upon. Thank you.

DR. GROSS: Thank you. The topic for discussion for the next two days is the effectiveness of the isotretinoin risk management program for the prevention of fetal exposure to Accutane and its generic equivalents, and to consider whether changes to this risk management program would be appropriate. Dr. Steven Galson will give our committees the charge. He is Acting Director of the Center for Drug Evaluation and Research.

Charge to the Committees

DR. GALSON: Thank you very much, Dr. Gross. I want to thank all of the committee members for being here. Your commitment to public service, indicated by the time commitment that you have agreed to make to this subject, is extremely important for the Food and Drug Administration and, indeed, very important for all the patients taking

this drug and our decision-making process.

Today and tomorrow you are going to hear details about the regulatory history of isotretinoin. You are going to review data that has been collected over the last few years about the Pregnancy Prevention Program, and you are going to help us by giving us advice about where this program should go in the future. These perspectives are extremely important to us. We can spend a lot of time talking to each other and tossing ideas around about what is the best course of action but when we have outside observers who have taken a fresh look at these programs it is enormously helpful to us as we move down the path to make decisions.

Isotretinoin has been on the market for about 22 years and it may take the record for the single drug with the most advisory committee meetings. I don't know if that is true but it is certainly very close. When Roche established the current S.M.A.R.T. program in consultation with the FDA in 2001, the agency established several goals

for the program. They were that no person should begin isotretinoin therapy if pregnant and that no pregnancy should occur while a woman is taking isotretinoin.

I want to just note that although those were the goals, the agency is very cognizant of the fact that setting a zero goal as a metric for something that really depends on human behavior for success and is probably not possible to attain. It is good to set that goal but when these issues are totally out of the control of manufacturers, physicians or the agency it is really impossible to actually meet that, and we have been criticized for saying our goal is zero. I want to make it clear that we recognize that it is probably not attainable but we still think it is important to set these important goals because it helps us set the stage for figuring out what steps we want to take and we think that is very important.

Setting these goals and establishing metrics to get there is very consistent with one of the evolving foundations of CDER's risk management

program which is that risk management programs must be periodically evaluated for effectiveness. Efficiency in risk management is very important and, without measuring the effectiveness of the program and knowing whether we are getting adequate preventive power for the resources devoted we really don't know where to go in the future with this program, and it doesn't help us in terms of establishing and setting up new programs for additional drugs.

Manufacturers of isotretinoin have been challenged by the agency to work together to minimize adverse events related to this drug, and we are really extremely heartened by the degree of collaboration that has taken place to date and by the way the manufacturers are working together to look towards the future. We really expect this collaboration to continue and we think that the goal of minimized the teratogenic risk of this drug is something that we all share with all the manufacturers and we, again, want to congratulate and are very heartened by the degree to which these

groups have been working together. We look forward to hearing about how the S.M.A.R.T. program has worked and how the companies have been working in detail together.

I want to just talk about the committee now. We ask you to really remain focused on the purpose of this meeting, the risk management program for the prevention of fetal exposure. We are aware that there are other important safety issues related to this drug but we really are going to focus on prevention of fetal exposure in this meeting. We would like you to consider the data presented. We want you to consider the past risk management programs and their achievements, and we are really looking forward to your recommendations as to whether the program, as it now exists, should continue; whether it is as effective as it could be; and how we should enhance it or establish new or different tools. So, with that I will close and pass it back to the Chair. Thank you very much. We are looking forward to a great meeting.

DR. GROSS: Thank you, Dr. Galson. You

are keeping us on time, setting a high target. The next speaker is Jill Lindstrom, a medical officer for the Division of Dermatologic and Dental Drug Products at the FDA, who will talk about the background and regulatory history of this medication.

Background and Regulatory History

DR. LINDSTROM: Good morning.

[Slide]

My objectives this morning are to set for you a clinical context for the use of isotretinoin; to outline the history of risk management efforts for this drug; to describe the current risk management plan in some detail; and to provide the committee with some rough guidelines for their assessment of the data that will be presented.

[Slide]

Isotretinoin is an oral retinoid that is indicated for the treatment of severe recalcitrant nodulocystic acne. It is the only drug moiety approved for this indication, although there are other oral related products in development. The

innovator was approved in 1982 and three generic products have recently entered the market.

[Slide]

This patient has nodular acne, a devastating disease that can result in significant scarring and permanent disfigurement. You can see that he has many lesions, to include large fluctuant nodules on his forehead, his cheeks, his chin and his nose.

[Slide]

This patient also has nodular acne and, again, you can see the many lesions on his face, the large fluctuant nodules extending down onto his trunk.

[Slide]

This is the same patient, a view of his back.

[Slide]

Again, a view of that patient's face prior to isotretinoin therapy--

[Slide]

--and following conclusion of a course of

isotretinoin therapy--he is dramatically improved.

[Slide]

And a third clinical example of a patient with severe nodular acne. Again, you can see the nodules, sinus track formation and scarring. This is the patient prior to a course of isotretinoin therapy--

[Slide]

--and at completion of his course of therapy.

[Slide]

Because of its unique effectiveness, current practice standards have expanded the use of isotretinoin to the setting of non-nodular but still scarring acne.

[Slide]

This patient does not have nodules, does not have classic nodular acne. She has severe papulopustular acne and her disease is scarring. You can also imagine that, in addition to the cutaneous morbidity, she has significant psychosocial morbidity from her disease. This is

her presentation prior to treatment with isotretinoin--

[Slide]

--and her result at conclusion of therapy.

[Slide]

And a second patient, again without nodular acne but with severe scarring papular acne. This is a front view--

[Slide]

--and a side view prior to treatment with isotretinoin--

[Slide]

--and the patient's result at conclusion of therapy, again dramatically improved.

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Now, isotretinoin is unique among the therapies in the acne armamentarium in that it addresses all four of the known pathogenetic mechanisms of acne. It decreases sebum production and shrinks the size of the sebaceous glands. It normalizes follicular hyperkeratinization and reduces follicular plugging. It decreases P. acnes

colonization, although not through a direct antibacterial mechanism but probably through making the micro climate of the follicle inhospitable to the organism. Finally, it is mildly anti-inflammatory.

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These events can be seen in this histological specimen, this biopsy of a comedo prior to isotretinoin therapy. You can see the dilated follicle filled with keratinous debris, the large sebaceous glands. Not well appreciated in the black and white photograph is the perifollicular inflammation and the numerous bacteria in the follicle.

[Slide]

In a biopsy of a follicle following isotretinoin therapy the sebaceous glands--again, I regret that I don't have a pointer but the sebaceous glands are much smaller in size; the follicular lumen is narrow. There is no follicular plugging and there is an absence of perifollicular inflammation.

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Isotretinoin is also unique in that a course of therapy is temporally circumscribed. Other anti-acne agents have no long-term impact and are effective only while they are being used. A course of isotretinoin, however, can result in complete and prolonged disease remission. Thus, patients with severe scarring acne like the clinical examples that I just showed you prior to the approval of isotretinoin would have faced years, perhaps even decades, of therapy with oral antibiotics in combination with topical agents. Now such patients, after a course of isotretinoin therapy, will see their disease become quiescent and the progression of their disfigurement halted, and they are spared the risk, the expense and the inconvenience of years of oral and topical therapies.

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However, isotretinoin does present its own risks. It is a known human teratogen. In utero exposure to isotretinoin can result in an increased

risk of spontaneous abortion and premature births, as well as structural abnormalities. Approximately 28 percent of exposed fetuses will have sufficient stigmata at the time of birth to be diagnosed with retinoid embryopathy. Additionally, many babies who are exposed to isotretinoin in utero will appear normal at birth and will go on later in life to manifest neurodevelopmental deficits.

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What has been done to manage this risk? At the time of approval in 1982 it was understood from animal data that isotretinoin was likely a teratogen, and in labeling the drug was classified pregnancy category X. Prescribers and patients were advised in the contraindications, warnings and precautions sections of labeling not to become pregnant while using the drug.

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The first report of a human malformation following in utero exposure to isotretinoin was published in 1983. In response, red warning stickers were distributed to pharmacies to be

affixed to each isotretinoin prescription that was dispensed. Additional reports of exposed pregnancies were received raising the concern both in the agency and the manufacturer. Multiple "dear doctor" letters were issued to inform the medical community of this risk and the label was revised as information became available.

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In 1988 the sponsor proposed a multi-tiered program to augment the risk management plan which they entitled the Pregnancy Prevention Program. An advisory committee was convened to review this proposal. There were, as I said, multiple components. First, the label was altered to include warnings printed directly on the package, and the "avoid pregnancy" icon was introduced, the familiar red circle with the slash and the pregnant figure. And, the packaging was changed to blister packaging.

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The package insert was updated to include a boxed warning informing physicians and patients

of a need for a negative pregnancy test seven days before treatment initiation; the importance of using two reliable forms of contraception; waiting to begin therapy until the second or third day of the next menses; and limiting the supply dispensed to 30 days; and the importance of repeating pregnancy testing and contraceptive counseling on a monthly basis.

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An informed consent form for females was introduced in that program. A kit for prescribers was provided to explain the details of the program, and the first iteration of the voluntary patient survey was introduced at that time. Additionally, there was a tracking survey to assess prescriber use of the program. That advisory committee recommended approval of the Pregnancy Prevention Program and the program was implemented in 1989.

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What was the impact of the program? It is somewhat difficult to say. From the time of approval of isotretinoin in 1982 pregnancies have

been reported to the agency. At the time of the introduction of the Pregnancy Prevention Program we gained a new tool to gather information about pregnancy reports, the patient survey. Those pregnancy reports are represented by the light blue bars from 1989 on.

Both of these reporting mechanisms, spontaneous reports as well as reports through the survey, are voluntary reporting mechanisms and so it is difficult to ascertain an accurate pregnancy rate. I want to remind you that this is a historical view prior to the implementation of the current risk management program, but what we can say is that the public health burden from exposed pregnancies continued to be large.

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Additionally, during this time or during the '90s Accutane use was increasing significantly. Because of these reasons, the large public health burden from exposed pregnancies as well as the increasing use, an advisory committee was convened again to consider augmentation of the risk

management plan.

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This advisory committee was convened in September of 2000 and they determined that there was, indeed, a compelling need for augmentation of the risk management plan. The agency agreed and this was communicated to the sponsor in a letter dated October 6, 2000. This letter has been included in the briefing package for the committee.

[Slide]

In this letter risk management is addressed from two perspectives, both pregnancy prevention and potential neuropsychiatric adverse events. Pregnancy prevention is the focus of this advisory committee. However, since the letter was included in your packet and does address neuropsychiatric risk management I want to briefly update the committee on the status of risk management efforts with regards to potential neuropsychiatric risk.

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Three points of action were recommended by

the committee and communicated in that letter. First, that the informed consent be amended to inform patients of the potential for neuropsychiatric adverse events, and this has been done. Second, it was advised that an educational program for prescribers be implemented, and this has also been done. Third, it was recommended that a comprehensive research program be undertaken to include clinical trials.

The sponsor submitted clinical protocols to investigate neuropsychiatric risk to the agency. When the agency reviewed them and gave the area some additional considered thought it was recognized that more basic science groundwork needed to be done before moving on to clinical trials, and this basic science groundwork is now being undertaken in collaboration with the National Institute for Mental Health. As that data is accrued we will move on at the appropriate time to clinical trials.

That is all I am going to say today about risk management of neuropsychiatric risk. I want

to remind both the committee and the public that it is not the subject of this advisory committee.

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Moving on to pregnancy prevention, also addressed in that letter, two goals, as Dr. Galson already mentioned, were articulated. The first, that no one should begin isotretinoin therapy if they are pregnant and the second, that effective pregnancy prevention would occur throughout the course of isotretinoin therapy. Implied in these two goals is that we would have the ability to assess whether or not they have been achieved.

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To achieve these two goals, five points of action were advised: augmentation of patient education; registration of all patients; registration of prescribers; implementation of a pregnancy registry; and linkage of prescription dispensing to adequate pregnancy testing.

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The agency and the sponsor, having heard the committee's recommendations, entered into

extensive discussions and negotiations in an attempt to design a plan that would incorporate the five points of action to achieve the two goals that had been articulated.

However, obstacles were encountered, particularly regarding patient privacy issues and compliance with the newly passed Health Insurance Portability and Accountability Act. Eventually, however, a plan was crafted and was approved in October, 2001. The innovator was the only product on the market at that time and they named their risk management plan S.M.A.R.T., a System to Manage Accutane-Related Teratogenicity. I will refer to their plan and the subsequent generic risk management plans as the current risk management plan so when I use the term the current risk management plan, you can think of that as interchangeable with S.M.A.R.T., S.P.I.R.I.T, I.M.P.A.R.T., etc.

I want to now move and describe how the plan that was crafted sought to incorporate those five points of action and then I will describe for

you the mechanics of the plan in some detail.

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The first point of action articulated by the committee was a heightened educational program for each patient that included verifiable documented written informed consent. This is fairly straightforward and is a component of the current risk management plan.

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The second point was complete registration of all patients, both male and female. This was intended to provide the denominator for ascertainment of the pregnancy rate. However, registries raise issues regarding patient privacy. The sponsor proposed an alternative proposal to estimate the denominator using pharmacy databases and survey data. This, of course, would avoid those patient privacy issues but the accuracy of the alternative proposal was dependent on increasing the survey response rate. The sponsor felt that this would be achievable.

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The third point of action was complete registration and certification of all prescribers. The sponsor objected that they did not have the authority to certify prescribers and so a plan of voluntary registration was devised in which prescribers self-attest that they possess the relevant competencies needed to safely prescribe isotretinoin. Additionally, prescribers singed a commitment to use the current risk management plan. The sponsor does provide prescribers with information about the plan, but the responsibility for obtaining the necessary education to achieve the relevant competencies rests with the prescriber. I will detail these competencies in a few moments.

[Slide]

The fourth point of action was a comprehensive plan to track fetal exposures to isotretinoin to include a formal pregnancy registry. This was intended to provide the numerator for ascertainment of the pregnancy rate. Again, because it involved a registry, it raised

concerns regarding patient privacy and issues regarding compliance with the newly passed HIPPA.

Again, to avoid these obstacles and to speed the implementation of augmented risk management measures, the sponsor proposed extrapolation of the numerator from survey response data. Accurate extrapolation from survey response data would require an increased survey response, which the sponsor identified as an increased response rate of greater than 60 percent. Now, they did feel that this would be achievable and, in order to achieve the increased rate, they planned targeted education of prescribers to increase awareness of the survey and they increased reimbursement for patient participation by 300 percent.

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The final point of action advised by the committee was the linking of dispensing of isotretinoin to verification of adequate pregnancy testing. This is accomplished in the current risk management plan through the use of yellow

qualification stickers. The physician verifies the negative pregnancy test and fills out the qualification sticker. The patient takes the prescription with the qualification sticker to the pharmacist who then verifies that the patient has, indeed, been qualified. However, in the current plan the pharmacist does not independently review the negative pregnancy test lab report. Pharmacist participation in the current plan is voluntary but encouraged through the way that the plan is designed.

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I want to take a moment now and describe in some detail the mechanics of how the current risk management plan works. It can be a bit complex if you haven't used it yourself in a clinical setting. The program begins with a physician who decides that they would like to prescribe isotretinoin and that they possess the relevant competencies necessary to do so.

The physician will sign a one-time letter of understanding with the manufacturer, attesting

that they do possess the necessary knowledge and experience in order to safely prescribe the drug, specifically that they are knowledgeable about the different forms of acne and its treatment; that they are knowledgeable about isotretinoin and its risks for teratogenicity; that they are knowledgeable about the risks for and the prevention of unplanned pregnancy; and finally, that they are knowledgeable about the current risk management plan and that they agree to use its mechanisms.

When the manufacturer receives this signed letter of understanding, they then forward to the prescriber the qualification stickers and separate educational materials for both the prescriber as well as for patients. Prescriber educational materials consist of things like best practices guides that inform the prescriber how to use the components of the current risk management plan. Educational materials for patients include things like brochures and videos.

The physician then encounters a patient

for whom they believe treatment with isotretinoin is indicated. From this point forward, as I am describing the mechanics when I refer to a patient I am speaking specifically of a female patient. So, when the prescriber encounters a patient for whom isotretinoin is indicated the first thing that they will do, having made the preliminary decision to prescribe the drug, is obtain a screening pregnancy test. They would also provide educational materials to the patient and the informed consent forms, which I will talk about in a minute.

Also at this time, contraception counseling and contraception would be provided. This can be accomplished in one of two ways, the prescriber him or herself, if they possess the necessary expertise, can provide the counseling themselves or they can refer to a reproductive health specialist such as a gynecologist for provision of the contraception counseling and the contraception. The female patient, unless they select complete abstinence, must be on two forms of

contraception, at least one of which must be a primary form, for 30 days prior to the initiation of isotretinoin therapy.

The patient reads the educational material, obtains the contraception counseling and the contraception and reads through the informed consent documents, signs those and returns them to the physician. There are actually two informed consent documents. The first is an informed consent/patient agreement which is given to both male and female patients. This outlines the risks for teratogenicity, as well as the potential risk for psychiatric adverse events, and also elicits agreement from the patient that they will abide by the risk management principles of the current risk management program, such as that they will not share their isotretinoin with other people; they will not give blood until at least 30 days after the conclusion of their therapy; that they will return to their physician on at least a monthly basis. The second informed consent document is specific for female patients and goes into much

greater detail about the risks of unplanned pregnancy and the risk of teratogenicity with isotretinoin therapy.

Both of those informed consent forms and the informed consent/patient agreement need to be signed and returned to the physician. Additionally, before prescribing isotretinoin the physician must obtain a second pregnancy test, this time timed to the woman's cycle within the first five days of the menses or, if the patient is amenorrheic, at least 11 days after the last episode of unprotected intercourse. After these steps have been accomplished the physician then fills out the prescription form, affixes the qualification sticker and fills that out with the date of qualification signifying that two negative pregnancy tests have been obtained; that the patient understands the risk management program; that adequate contraception, either two forms or absolute abstinence, have been initiated.

The patient then takes the prescription with the qualifying sticker affixed and filled out

to the pharmacist. The pharmacist verifies that the sticker has been affixed, has been properly completed, and also that the receipt of this sticker and the dispensing of the isotretinoin occur within seven days of the date of the physician's qualification of the patient. If all of those criteria are met the pharmacist dispenses the isotretinoin along with a medication guide which is an information brochure for patients which, by law, must be dispensed each time isotretinoin is dispensed that describes in layman's language the risks of the drug and the steps that need to be taken to minimize those risks.

The patient then initiates their course of isotretinoin therapy and on a monthly basis will return to the prescriber to be requalified. Requalification consists of repeating the pregnancy test and verifying that the test is negative; re-counseling the patient regarding contraception; and ensuring that the risk management program is being abided by.

We receive data about the program from several sources, first, spontaneous adverse events reports come to the agency from physicians, the manufacturer, from patients as well as from pharmacists. Additionally, the patient is encouraged to participate in the voluntary patient survey and data is gathered through that mechanism. Finally, pharmacies are surveyed and the prescriptions are audited to check for compliance with the sticker program.

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The risk management plan, as I have described, was approved for the innovator in October of 2001. Since that time three generic products have been approved and have entered the market. Their risk management plans are identical in the essential elements that I have just described to the innovator plan. So, again, when I speak of the current risk management plan, that would be interchangeable for either the innovator plan or the plan of the three generic products.

[Slide]

However, while the four risk management plans are identical in their essential elements and can be considered interchangeable, there are some differences that have caused marketplace confusion. Besides having different trade names for the four drugs, each manufacturer has elected to name their risk management program by a different name so for Accutane with have S.M.A.R.T., the System to Manage Accutane-Related Teratogenicity. For Amnesteem we have S.P.I.R.I.T, the System to Prevent Isotretinoin-Related Issues of Teratogenicity. For Sotret it is I.M.P.A.R.T., Isotretinoin Medication Program Alerting you to the Risks of Teratogenicity. For Claravis it is A.L.E.R.T, the Adverse Event Learning and Education Program Regarding Teratogenicity. Additionally, different survey contractors have been employed by the innovator who uses Degge/SI and the generic firms who all use the Slone Epidemiology Unit. Finally, mid-course changes by the patient's pharmacy provider in brand of isotretinoin dispensed can result in patient confusion and perhaps multiple

enrollment in the voluntary survey.

[Slide]

When this current risk management plan was approved the sponsor was instructed to submit a comprehensive report on the metrics of the program after one year of implementation. This advisory committee has been convened to comment on those data. The advisory committee in 2000 did not address benchmarks nor define success. Indeed, to do so is challenging. But at this time I want to provide you with some rough guidelines that you can use as you are thinking about three parameters in particular, the survey response rate, the sticker use and the number of fetal exposures.

[Slide]

The survey response rate, by the sponsor's own assertion, would need to be greater than 60 percent. The success of the current risk management program in terms of accurate estimation of that numerator for the pregnancy rate is dependent on this higher survey response rate. The agency's approval of the current risk management

plan was based on the sponsor's assertion that they would be able to achieve this threshold.

[Slide]

The qualification stickers serve as a surrogate endpoint for the use of the current risk management plan. When the agency approved the plan it was understood that the stickers were an imperfect surrogate and, in fact, as the data has come in they may be more imperfect than we had realized, and other speakers will describe to you the linkage between the stickers and various components of the program such as pregnancy testing. However, at the time of approval the sponsor was informed that because the sticker served as a surrogate, and an imperfect surrogate at that, the threshold for success would be very, very high and, in fact, would approach 100 percent in terms of sticker use.

[Slide]

Finally, and perhaps most importantly, fetal exposures--it would be difficult to identify an acceptable number for fetal exposures. In

considering what success would look like in terms of fetal exposures the committee may want to think of this in parallel with the two goals that were articulated by the 2000 advisory committee, the first goal being that no one initiate isotretinoin therapy if pregnant. This goal, the responsibility for which rests largely on the shoulders of prescribers, may best be achievable.

The second goal, that no one become pregnant while on isotretinoin therapy, is more complex because it depends on patient behavior. Again, in considering the threshold of success in terms of fetal exposure you may want to think of these two populations independently, and also in considering what risk management tools would impact these populations you may want to consider them separately as different tools may be appropriate.

[Slide]

In summary, isotretinoin is a uniquely effective drug for the treatment of severe, scarring acne, a truly devastating disease. There has been a long history of risk management efforts

to prevent fetal exposures to this drug which were built sequentially. The current risk management program has introduced some new tools and the advisory committee is being asked to comment on the effectiveness of these new tools and the current program.

I and my colleagues look forward to hearing your considered input on the data and how we can optimize the public health by ensuring that isotretinoin is available to the patients who needed it in a context that minimizes and best manages the risks. So, I thank you for your attention this morning and I would be happy to take your questions.

DR. GROSS: Thank you very much, Dr. Lindstrom. Before the questions, I would like to introduce an additional consultant who will be participating in our joint advisory committee session, Dr. Vega. Dr. Vega, would you please introduce yourself?

DR. VEGA: Yes, good morning. I am a Board-certified pediatrician with a Masters in

Public Health and a Fellowship in Pharmacoepidemiology from the Food and Drug Administration. I am also a former medical epidemiologist from the Office of Drug Safety, with extensive experience with the isotretinoin pregnancy prevention issue. I presented at the last advisory committee the data on the different options to modify the Pregnancy Prevention Program. I currently work for PSI International in their adverse event reporting project.

Questions from the Committee

DR. GROSS: Thank you. Now Dr. Lindstrom will entertain questions from the committees. Yes?

DR. CRAWFORD: Dr. Lindstrom, thank you for the overview. In terms of considering possible risk management tools to enhance pregnancy prevention, one thing I am not sure of after reading all the materials we were provided is whether the reasons for failure have been identified. So, has there ever been any thought given to some type of failure mode analysis determining for those patients who do become

pregnant, exactly what went wrong so efforts could be targeted on preventing those failures in the future?

DR. LINDSTROM: That is an excellent question. The speakers that follow will be addressing the data and I believe also, as much as we know, the reasons for failures. So, if you don't mind, I think I will defer the answer to that question to the presentations that will follow mine.

DR. GROSS: Dr. Gardner?

DR. GARDNER: Dr. Lindstrom, could you give us some idea of the epidemiology of the severe acne for which these drugs are both specifically indicated and also for which they are being used? For example, can you tell us the incidence or even the prevalence of the condition in the population and the distribution by gender and by age, if you know?

DR. LINDSTROM: I will do my best to answer that question. Acne is extremely common, particularly in the adolescent age range. The

incidence has been reported to be 80 percent in the 12-20 year-old group and falling to about 3 percent in the over 45 year-old age group. You can sort of extrapolate the decrease during that time.

DR. GARDNER: Is that severe acne?

DR. LINDSTROM: No, that is all acne. There is not an ICD-9 code for severe acne so it is difficult--I don't actually know and I couldn't find, in preparing for this committee meeting, an incidence or a prevalence for severe acne. I can tell you that recalcitrant nodular acne is not the majority of acne. Severe scarring acne is a larger proportion of acne patients. As a practicing dermatologist, it was not uncommon. I saw scarring acne on essentially a daily basis but I don't have incidence or prevalence figures for you, other than the prevalence of acne in the population at large.

DR. GROSS: Sarah Sellers?

DR. SELLERS: A quick question on the qualification in the current program, the qualification sticker that goes to the pharmacy has a qualification date on it?

DR. LINDSTROM: Yes.

DR. SELLERS: And, is that date the date of the confirmed negative test?

DR. LINDSTROM: Yes, it is. For initiation of therapy it would be the date of the second confirmed negative pregnancy test and for ongoing therapy it would be the date of the repeated negative pregnancy test.

DR. SELLERS: It is not the date that a sample was taken for a pregnancy test?

DR. LINDSTROM: No, I believe it is the date--I am sorry, I didn't follow actually your question.

DR. SELLERS: The qualification date is actually when the negative result is received--

DR. LINDSTROM: That is my understanding.

DR. SELLERS: --not the date a sample is drawn for analysis to go to the lab?

DR. LINDSTROM: Correct.

DR. SELLERS: Thank you.

DR. GROSS: Yes, Robyn??

DR. SHAPIRO: I guess I am curious about

the HIPPA problem that you have found with some of the registry ideas. Why couldn't the patients simply authorize release of particular information in order for them to get the drug and, therefore, make that information available?

DR. LINDSTROM: At the time of the prior advisory committee and at the time that the agency and the sponsor were working to craft the plan, HIPPA had just been approved and towards the end of that time period was being implemented. In working with consul from the company as well as consul within the agency, working out the details of HIPPA compliance proved difficult and while it probably would have been achievable, it was taking a lot of time. So, the sponsor proposed and the agency approved these alternative methods in order to have a plan in a more timely fashion that could be implemented that could augment the risk management program. As understanding of compliance of HIPPA has matured, I think it would be much easier to navigate those waters at this time but at that time the Act had just been passed and was in the process

of being implemented and understanding was not yet mature.

DR. GROSS: Dr. Bigby?

DR. BIGBY: I have two questions. The first one is that you stated that some patients who take Accutane never have acne again. Are you or someone else going to actually tell the committee what the actual numbers are in terms of the long-term efficacy of Accutane?

DR. LINDSTROM: What I had hoped to state was that patients may achieve complete and long-term remission. I have read different figures. Approximately 10-20 percent of patients who are treated with Accutane never require treatment with Accutane again. Another way to state that would be that 10-20 percent of patients who undergo a course of isotretinoin therapy do require a second course of isotretinoin therapy. Of the 80-90 percent that only require one course of isotretinoin therapy, a portion of those are then able to be maintained with no treatment at all. A portion would require only topical therapy and some may require oral

antibiotic therapy.

DR. BIGBY: I just think that it is important for the committee to know actually what those proportions are and I just hope somebody brings that data to the table.

DR. LINDSTROM: I don't have those numbers. All I can tell you is that between 10-20 percent of isotretinoin patients do undergo a second course of therapy.

DR. BIGBY: Well, those numbers do exist and I just hope it is sort of made known to the committee what those numbers are.

The other question I had was of the pregnancies that occurred prior to S.M.A.R.T. and during S.M.A.R.T., is there any data about who the prescribers were?

DR. LINDSTROM: I am sorry, can you repeat your question?

DR. BIGBY: You presented information about pregnancies that occurred for the year prior to S.M.A.R.T. and during a year of S.M.A.R.T. What I would like to know is who the prescribers of

Accutane were for those women who got pregnant.

DR. LINDSTROM: Yes, actually I did not present any data about pregnancies during S.M.A.R.T. My objectives at this point of the day were to set the historical context so the slide that I showed was that reported pregnancies to the agency were from 1982 through 1999. Speakers later today will update you with the current pregnancy data, the more recent data during the implementation of the current risk management program.

Now, there were two parts to your question and I only answered half. Can you tell me again the second part of that question?

DR. BIGBY: No, you answered it.

DR. LINDSTROM: Okay.

DR. GROSS: Dr. Michael Cohen?

DR. COHEN: Earlier you mentioned that there may occasionally be some confusion between the various risk management programs for isotretinoin that exist and perhaps also the brand names. Are you saying that that occasionally

contributes to some of the problem that we are seeing with isotretinoin and the way that it is handled? Also, who actually does the selection? Is it the prescriber or the pharmacist? Is it a substitution that is made? I didn't understand that.

DR. LINDSTROM: In stating the various names and alluding to confusion, my point is just to give the perspective of patients and prescribers. It is a somewhat complex plan and there are various names out there, and to just make the committee aware that that is a potential source of confusion, the multiple names for the risk management plans. I did not mean to imply that there should not be different trade names for the products of the various manufacturers but, rather, that the risk management plan having multiple names does present some confusion for patients. The second part of your question?

DR. COHEN: Well, I guess I am a little bit confused about who actually selects the brand that will be used. You mentioned that occasionally

a patient can go from one brand to another--

DR. LINDSTROM: Right.

DR. COHEN: --does that contribute to any confusion that we should be concerned about? I understand the plans are pretty much the same.

DR. LINDSTROM: Right.

DR. COHEN: They have the same baseline requirements but are there any errors that this contributes to that, you know, might have an adverse outcome that we should know about?

DR. LINDSTROM: Sure.

DR. COHEN: In other words, should there be one plan?

DR. LINDSTROM: I think that is an excellent question and one that the committee will need to be considering as the day goes forward. Other speakers will present to you the details of the data that has been obtained from the current risk management plan and will be in a better position to address confusion from the agency's perspective in terms of data collection from multiple plans.

As far as whether a patient receives one particular manufacturer's isotretinoin or another, a physician can specify that as they write the prescription but I think in many instances it is the pharmacy provider that makes that determination of which patient receives which brand. So, it is a little bit outside of the prescriber-patient relationship.

DR. GROSS: Dr. Kweder?

DR. KWEDER: Yes, I think I can clarify a little bit. We do not have specific data on the frequency of switching between brands. We have heard for patients and providers that this is a potential source of difficulty but we do not have data saying how common it is for patients to be required to switch mid-course. Just like any medication, the source of imposing a change could be anything from the patient wanting a cheaper brand to the pharmacist pressing for that, or the physician or even the health insurance plan that will only pay a certain amount.

DR. GROSS: Dr. Trontell?

DR. TRONTELL: I was going to just elaborate on Dr. Kweder's remarks. We don't yet have any data to document that confusion has occurred between these programs.

DR. GROSS: Thank you. Dr. Whitmore, did you have a question?

DR. WHITMORE: The answer came up already, thank you.

DR. GROSS: Dr. Day?

DR. DAY: Was any provision made for providing the risk management plan for mail order prescriptions? I assume that originally Accutane was available through mail order.

DR. LINDSTROM: The prior risk management plan did allow for mail order prescriptions. For the current risk management plan, as I understand it, a mail order prescription might be challenging in that the drug needs to be dispensed within a seven-day window of qualification. Not only that, but there are other features of the plan that might not happen. So, it is not allowed.

DR. GROSS: Dr. Honein?

DR. HONEIN: I just want to follow-up with some questions on the multiple risk management programs. I wondered if there was any data on how often women get one set of information from a prescriber and a different set of information from the pharmacist at the time it is dispensed, and if there are any reports of that contributing to confusion.

DR. LINDSTROM: The information that the patient receives from the pharmacist would be the medication guide which would be the same for all of the manufacturers' products, the innovator as well as the generic. The pharmacy has the option of providing additional patient education information that is not part of the current risk management plan that would be in addition to that.

DR. HONEIN: Don't they get enrollment forms both from the prescriber and the pharmacy, and wouldn't those be different if they got different sets of material?

DR. LINDSTROM: Thank you. That is a good point. The enrollment forms are included with each

prescription that is dispensed and the enrollment form for the innovator uses one contractor and the enrollment forms for the generics utilize a different contractor so you are correct that that would be another potential source of confusion for a patient.

DR. GROSS: Dr. Knudson?

MS. KNUDSON: I am curious about the age distribution of the women taking the drug. I would like to know does the enrollment form or the survey form or the qualifying sticker carry the age?

DR. LINDSTROM: The qualifying sticker does not. Age may be obtained by the pharmacy as part of an independent pharmacy data collection with age, date of birth and so forth to ensure that the correct prescription is dispensed to the correct patient. Age is a component of the voluntary patient survey.

DR. GROSS: Dr. Ringel?

DR. RINGEL: This is a quibbling point from the "nothing in life is perfect" department. You mentioned that it should be possible to prevent

initiation of isotretinoin therapy before a pregnancy, and there are ways you can actually manage it if you consider that there is a certain number of false-negative pregnancy tests, particularly early in pregnancy, and also there can be confusion with bleeding at implantation and bleeding for other reasons with menses. If you put those together, in fact, it would be possible to be pregnant, despite all of our efforts, before initiating Accutane.

DR. GROSS: Dr. Strom?

DR. STROM: In the era of increasing computerized data entry, how would this risk management plan work?

DR. LINDSTROM: I am sorry, can you elaborate on your question?

DR. STROM: Sure. The current risk management plan, as I understand it, relies on a sticker program.

DR. LINDSTROM: Yes.

DR. STROM: There is increasing use of computerized prescribing and a big push nationwide

to increase that.

DR. LINDSTROM: Yes.

DR. STROM: How could this be operationalized? How could this plan possibly work in that context?

DR. LINDSTROM: The current risk management plan does not allow for computerized prescriptions.

DR. STROM: Just to clarify, given the current environment in pharmacy, neither mail order nor computerized prescriptions are compatible with the current plan.

DR. LINDSTROM: Computerized prescriptions are not compatible with the current plan and I think mail order would be difficult with the current plan. Again, I have set the historical context and described the current plan.

DR. GROSS: Dr. Kibbe?

DR. KIBBE: I have just a question about the two figures that you gave us and the data that is contained therein. Have you taken the number of reports of pregnancies for the years from '91 to

'99 and divided them by the number that you show for the number of female patients during those same years and gotten, even though it is an inaccurate number, at least an estimate of number of pregnancies per 1,000 patients over that time frame?

DR. LINDSTROM: I believe that you are bringing up the issue of pregnancy rate. While the absolute number of pregnancies reported to the agency was relatively constant, the number of women receiving isotretinoin prescriptions was rising. I don't want to belabor this point but there are two issues related to deriving a rate from the data that I showed. First, pregnancy reporting is voluntary, both the spontaneous reports and those received through the survey. They are voluntary. Both are voluntary mechanisms. We know that adverse event reporting declines over time and we know that it does not capture all events so it is an imprecise number.

Second, even if that numerator in terms of the number of pregnancies reported was reflective

of the total number of exposed pregnancies that had occurred, even if that number, indeed, did stay flat the public health burden of those exposed pregnancies, of those affected babies, was not declining. Those two slides were actually presented to the advisory committee in 2000, and for those reasons it was determined to be important to increase the risk management for this drug because the public health impact has remained significant.

DR. KIBBE: So, your answer is no?

DR. LINDSTROM: Yes.

DR. GROSS: Dr. Bull?

DR. BULL: I just wanted to remind you, going back to the issue of computerized prescriptions, that this whole risk management plan is predicated on a high level of interaction between the patient and the healthcare provider. These are non-refillable prescriptions. The patient has to return to the healthcare provider for an interaction, hopefully a face-to-face evaluation of how the acne treatment is

progressing, such that because of the fact that these are not prescriptions that are automatically refilled it is not a course of therapy where you are given a prescription that you renew for five months. It is one where every month during that course of time there is a need to return to the healthcare provider of record.

DR. GROSS: I am going to take the prerogative of the chair and declare a break at this particular time. We have no breaks scheduled for the morning and I think we will hold questions until a little bit later. Thank you. We will reconvene at 9:30.

[Brief recess]

Open Public Hearing

DR. GROSS: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, which we are about to start, the FDA believes that it is important to understand the

context of an individual's presentation. For this reason, the 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, the 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.

We have two registered speakers for the morning, Dr. Robert A. Silverman is first. Dr. Silverman?

DR. SILVERMAN: Dr. Gross, members of the advisory committee, thank you for giving me the

opportunity to speak about the continued availability of isotretinoin. My statement will focus on the benefits of this drug and the impact of pregnancy prevention risk management efforts on its availability to patients.

I have been practicing pediatric dermatology for nearly two decades. At first I was in Cleveland at Rainbow Babies and Children's Hospital. Since 1989 I have maintained a private practice in Northern Virginia and a dermatology clinic in the Department of Pediatrics at Georgetown University. For the record, I have not participated in any pharmaceutical company sponsored acne drug studies, nor am I taking any reimbursement from the AADA, and the only thing I have taken today is one bottle of water.

[Laughter]

I am a physician who treats patients, not a healthcare provider who sees clients. I make the distinction to emphasize the trust and close relationship between a physician and patient that is necessary for obtaining the best results when

treating acne while minimizing side effects of any of the medications that we use. As a pediatrician, I recognize the social and psychological impact that an acne-scarred body image has on teenagers. I know of no drug that has changed the lives of my patients with acne more than isotretinoin. It has been a Godsend to adolescents and to young adults with recalcitrant, nodular, nodulocystic and scarring disease.

Unlike dermatologists entering the medical work force today, I remember how we used to treat severe nodulocystic acne. One of the most painful, gruesome procedures that I learned in my training at the Children's Hospital in Boston was the incision and drainage of multiple purulent abscesses, like you saw earlier, on the faces of young men and women afflicted with recalcitrant nodulocystic acne. The procedure is nearly a historical footnote since we have the availability of isotretinoin.

There is not a week that goes by in my practice that a concerned parent, with facial scars

themselves, brings in a preadolescent with minimal or no acne for anticipatory guidance in hopes of their child avoiding the same fate that they had when they were growing up. Of course, the vast majority of these children never-ever reach the point of needing isotretinoin. But for the few who progress and require it, I am thankful that I have the option to use this medication. The reason I am here today is to keep this drug available to all people who need it.

Let me share a story that perfectly illustrates the wonders that can be worked by this drug. In 1982, when I was in Boston, the year that isotretinoin first became available in the United States, I met a beautiful young lady who had a beautiful complexion. During that year she developed inflammatory acne that then rapidly progressed to severe painful, nodulocystic disease. She was being cared for by an excellent dermatologist at one of the nation's first and premier HMOs. Minocycline, benzoyl peroxides, Retin-A and oral contraceptives made no difference

in her appearance.

Isotretinoin was not widely prescribed and it was not until 1986 when she saw her fourth dermatologist, after moving to Washington, D.C., that Accutane was offered to her. The years between 1982 and 1986 were for her filled with anxiety and self-consciousness. I know this because this woman is now my wife. She took isotretinoin safely. She was aware of the teratogenic risks and used two forms of birth control. We now have two healthy boys who were conceived well after my wife-to-be's finishing the drug. This story is obviously close to my heart but it also illustrates the fact that female patients of childbearing potential can and do use isotretinoin safely.

I have treated many teenaged girls and young women with isotretinoin. I have personally prescribed isotretinoin since 1986 and have used it according to the risk management guidelines with utmost caution, and since the S.M.A.R.T. program has been in effect I have complied with it to the

best of my ability.

As a clinician in the trenches, I am familiar with the difficulties and weaknesses that were outlined that may impede optimal participation in the S.M.A.R.T. program. Complicating and restricting access will only drive needy patients to obtain isotretinoin through illicit channels or those that circumvent well-established doctor-patient relationships. This would be a travesty of monumental proportions. In grade school I learned the acronym KIS--keep it simple. The more complicated you make the process of obtaining this medication the more mistakes are going to be made.

I would be happy to help in any way that I can to keep this medication available to all who need it and to address the small, but unfortunate, number of pregnancies that have occurred while on this drug. Thank you for your time and consideration and I would be happy to entertain any questions if we have a few seconds. Thank you.

DR. GROSS: Thank you very much, Dr.

Silverman. The next speaker is Dr. Sidney Wolfe of the Public Citizen's Health Research Group.

DR. WOLFE: Helping out in this presentation is Dr. Sherri Shubin who is a pediatrician and currently doing a preventive medicine residency at Johns Hopkins. She is spending part of her residency with us.

[Slide]

I will take a minute or so to go over the first couple of slides. Our involvement really started shortly after the drug came on the market in September of '83. We submitted a petition urging patient package inserts and black box warnings about birth defects and life-threatening adverse events. Prior to approval, as many of you know, there was a pretty comprehensive program to make sure that no one who got the drug got pregnant, and a number of those strictures were dropped at the time of initial marketing and slowly some of them were reintroduced.

On April 26, ADA testified before this committee describing Accutane as an imminent public

health hazard and saying that unless certain restrictions were imposed it should really come off the market. The restrictions are listed there, one of the most important of which is, of course, limiting prescribing to dermatologists who file sworn affidavits stating they will adhere to the stated indications for the drug. That is supposed to be happening, not the sworn affidavit part but, obviously the amount of prescriptions belies the fact that that is what it is limited to. We then filed a petition to the FDA in May of 1988 with recommendations, saying it should come off the market and only be allowed back on with these restrictions.

[Slide]

Just finishing up a little bit on that, we continued urging removal from the market unless restrictions were put in and, thus far, these restrictions just have not been put in. Most recently, in September, 2000, we testified that at that time the issue of depression and suicide had arisen and again we proposed restrictions.

[Slide]

This is testimony before this committee by Dr. David Erickson, who was then Chief at the Centers for Disease Control and Prevention of the Genetics and Birth Control Branch. His statements are very poignant because 15 years later the same issue is there: "The birth of babies with defects caused by fetal exposure to Accutane is unnecessary. FDA decision to allow the marketing of Accutane is a failed regulatory experiment. A decision to depend on better contraception alone, without active intervention to reduce the number of users, is a decision to leave the number of affected babies at an unacceptably high level." Finally, one of his suggestions was, "perhaps a formal IND," investigational new drug, "would be a suitable mechanism to reduce the frequency of Accutane embryopathy."

[Slide]

Now, these are data from the package that was provided to you a couple of weeks ago--it should have been included. This is an FDA

presentation before this committee back in September of 2000. What they said was that as of that time these are just the reported cases and, as several people said this morning and it understates the actual magnitude of the problem with 1,995 exposed pregnancies; 1,214 elective abortions; 383 live births; and 162 infants with birth defects.

[Slide]

These now are the more recent data from the first year of the S.M.A.R.T. program. Again, the first two points are taken directly from the package that was handed out and 156,800 "unique"--the phrase used in there--women were given the drug. Secondly, the estimated pregnancy rate, and I am sure this is on the low side but that is what was in this information set is 0.35 percent. If you take that rate and apply it to the number of "unique" women given the drug in that first year it means that there have been 548 pregnancies and this is 4.6 times higher than the voluntarily spontaneously reported pregnancies that are also listed in the package, which is a measure

of the under-reporting.

[Slide]

Of the 61 pregnancies with known outcomes--remember, about half of them had outcomes unknown--48 of 61 or 78.7 percent resulted in elective abortions. Again, if you apply this to the more likely estimate of the actual number of pregnancies, 548, this means that there would have been 431 elective abortions in that one year ending in March of 2003.

[Slide]

Again estimating the number of deliveries, of 61 pregnancies with known outcomes, 7 of 61 or 11.5 percent resulted in deliveries. There were some spontaneous abortions, and so forth that make up some of the other ones aside from the elective abortions. Again, applying this to the 548 estimated pregnancies, there would have been 63 deliveries. Using FDA's and the CDC's figure, which is probably on the low side, 25 percent birth defects and the 50 percent mental retardation is as close--there hasn't been any really careful study

on it but applying those figures to this estimate, we are talking about 16 infants with birth defects and 31 with mental retardation just in that one year.

[Slide]

The reason the S.M.A.R.T. program and even the new Roche proposal do not seriously address the two major issues here are as follows: In 1989 CDC estimated that there were no more than 4,000 women of childbearing age with severe cystic acne. They did not even get into the recalcitrant or other therapy. Adjusted for population growth because these were 1987 data, the number may now be 6,000. Given that there were 156,800 "unique" women of childbearing age who got the drug in that first year of S.M.A.R.T., this represents a 26-fold excess in prescribing over the number of on-label prescriptions.

The second point is that unless there is something more than a sticker and an assurance but there is actually the provision of a lab test showing that the woman, in fact, was not pregnant

and at least a description of the contraceptive methods--unless that happens, then people are going to have stickers that are misrepresenting what has actually happened.

[Slide]

The reason why we are about to file a petition in the next week or two asking for this drug to be taken off the market and made available through an IND is that there have been 20 years of failed voluntary and even more recently some mandatory restrictions, and they have led to actually a total of more pregnancy exposures because the actual amount of prescriptions has gone up. I think it was estimated in '88 or '89 that there may be 70,000 "unique" women of childbearing age getting the drug and it is now some 150,000.

As we recommended in '88 and the CDC itself suggested as an option the next year, as I showed you in Dr. Erickson's presentation, we now propose a ban on marketing with subsequent availability only under a tightly controlled IND as the only feasible way to significantly reduce

prescriptions and pregnancy exposures.

[Slide]

These would be the main elements of the restrictions in an IND: Photographic proof of severe cystic acne confirmed by an independent group of dermatologists. Digital cameras make this kind of process relatively easy to set up.

Secondly, a written record for each patient that there, in fact, is adequate previous treatment of the disease with antibiotics and other treatments and that there is recalcitrance to it.

Third, a written statement of contraceptive practices and provision of a copy of this and a negative pregnancy test in order for the drug to be dispensed each time.

[Slide]

In summary, the S.M.A.R.T. program is clearly a failure. Without these proposed IND restrictions, this administration and this advisory committee will continue to put its imprimatur on the reckless use of a drug that each year causes the need for hundreds of abortions and many

seriously deformed infants with birth defects and/or mental retardation. This is one of the two worst epidemics of preventable serious birth defects ever seen in the U.S. I would just point out the other one is two defects where there is deficiency of folic acid, as you know. The odds of neural tube defects are a couple of orders of magnitude lower than the odds of a birth defect with a live birth. Of course, it is different not to have enough folic acid as opposed to be administering one of the more potent teratogens we have ever seen. It is time to end the more than 20 years of voluntary restrictions and some mandatory ones that have failed to reduce its prescribing for more than 20 times as many women as would be using the drug if it were limited to the approved indications. Thank you. I would be glad to try and answer any questions.

DR. GROSS: Thank you very much, Dr. Wolfe. The final speaker in the open public hearing will be Dr. Sherri Shubin, who will read a letter from Dr. Furberg, which is in your packet.

DR. SHUBIN: Thank you. I have no financial conflicts of interest. As a member of the public, I would like to read the statement that was written by Dr. Curt Furberg, a member of this committee who could not be here today:

Due to an unexpected family health problem, I will not be able to attend the upcoming advisory committee meeting on Accutane risk management. Based on long observation and careful study, I feel very strongly about this issue and regret that I will not be there to express my views and participate in the committee's discussion and deliberation. As a member of the committee, I would ask that the following be read aloud at the meeting after all testimony has been presented but before the committee begins its consideration and discussion of the issue and the questions presented it by the agency.

To be candid, the history of Accutane is an example of inadequate and ineffective risk management by the FDA and the manufacturer of Accutane to the detriment of thousands of women.

Examples are numerous. Although Accutane was a known animal teratogen and a suspected human teratogen at the time of its approval, the company did not recommend and the FDA did not insist upon labeling that emphasized the importance of contraception or abstinence while under treatment with the drug. The consequences of this omission become more apparent when one understands that five women became pregnant while taking Accutane during pre-approval clinical trials despite following the contraception requirements of the study.

In 1988, a highly publicized FDA advisory committee meeting was held to discuss the high level of pregnancy exposure to Accutane and the overuse of the product and its contribution to the pregnancy exposure problem. The Pregnancy Prevention Program, PPP, emerged following this meeting as the primary means of managing Accutane's teratogenic risks. Several advisory committee meetings were held to monitor the progress of the PPP between 1989 and 1991. It was clear from these meetings that the majority of women taking Accutane

were not volunteering to participate in the PPP, that even in the group that did volunteer pregnancy testing was infrequently performed and that pregnancy exposure to Accutane was still occurring at a high level.

Remarkably, no advisory committee meeting on the Accutane pregnancy exposure and the performance of the PPP was convened until September, 2000. At this meeting, it was shown that enrollment in the PPP was low and falling, that pregnancy testing was still often not being performed and that recommendations about contraception or abstinence were often not adhered to. Even more alarming, the use of Accutane in women had increased three-fold during the preceding ten-year period when one would have expected it to decline substantially because of successful treatment of prevalent cases of severe nodular acne. The committee's response to this evidence was to declare the PPP a failure and to recommend that a comprehensive risk management program that included patient and physician registration, as

well as mandatory pregnancy testing, be established. None of these has been implemented.

Instead, the S.M.A.R.T. program was introduced. It is an effort that added yellow stickers to the existing PPP, but had no means of determining if pregnancy testing was actually performed or of how many pregnancy exposures actually occurred. Unfortunately, S.M.A.R.T. had the same basic design limitations as the PPP and this should have been recognized. Now, after almost four years and thousands more of unnecessary pregnancy exposures to Accutane, this committee is once again asked to advise the FDA.

Simply put, I believe that the system is not safe and cannot be used in a safe manner. To minimize the number of pregnancy exposures to isotretinoin an IND-like process could be implemented that ensures universal pregnancy testing, registration of all pregnancy test results and incorporates a mechanism whereby the drug cannot be dispensed without a negative pregnancy test. This coupling of a negative pregnancy test

with dispensing of the drug would be analogous to the policy that has been successfully employed with the antipsychotic clozapine and has been summarized as "no blood, no drug." An added benefit of such an approach would be that we would have more accurate information regarding the actual number of pregnancy exposures to the drug. The numbers we have now, coming from a relatively small and self-selected group of volunteers, is undoubtedly a gross underestimate of reality.

Other features of this IND-like approach could include limiting the number of isotretinoin-dispensing centers, mandatory pregnancy avoidance counseling at each visit and the proviso that dispensing centers would be audited periodically. An important objective of our risk management should be to reduce the overuse of isotretinoin. Therefore, I would recommend that the IND-like process I have briefly described include some means of documenting the presence of severe nodular acne in patients being considered for isotretinoin treatment. In clinical trials for

the approval of Accutane only patients with severe cystic acne were enrolled, and photographs of at least some of these patients were taken and used in advertisements and at professional meetings. Perhaps a photograph, documenting the patient's severe cystic acne, could be required prior to approval for treatment.

The S.T.E.P.S. program for thalidomide has been talked about as a possible model for isotretinoin risk management, but it would not be adequate. If my understanding is correct, there is actually no current coupling of a negative pregnancy test with dispensing of the drug and there is no central registry of the pregnancy test results. Under this system, thalidomide prescribers answer several questions over the telephone in response to automated prompts in order to receive a number authorizing use of the drug for the next month. This system is very similar to the yellow sticker system under S.M.A.R.T. in that it relies on prescriber self-attestation. There is no validation that what the prescriber has answered is

true and there is no comprehensive or reliable means of knowing how many pregnancy exposures have occurred.

The occurrence of pregnancy exposures with the original Accutane pre-approval clinical trials and, more recently, within a clinical trial for another formulation of isotretinoin raises an uncomfortable question, should this drug have ever been released on the open market? I think it was and is unethical to allow isotretinoin to be available for use outside of the protections that would be afforded by a controlled and documentable process of distribution.

I do have copies of this statement for anyone who would like one.

DR. GROSS: Yes, there are copies of the statement in the committee's folders. Thank you very much, Dr. Shubin. Shalini Jain has a comment she would like to make now.

MS. JAIN: I just want to make a comment for a point of clarification with regards to Dr. Furberg's letter. Dr. Shubin was reading the

letter on behalf of Dr. Furberg. In functioning as an FDA committee member representative, he has not been cleared for this meeting for purposes of conflict of interest but solely as a representative of the public today. Thank you.

DR. GROSS: Thank you. We will now move on to the next set of presentations. From Hoffmann-La Roche, Joanna Waugh, Group Director for Regulatory Affairs, is first; Dr. Martin Huber, Vice President, Global Head, Drug Safety Risk Management; and Dr. Susan Ackermann Shiff, Global Head, Risk Management, Drug Safety Risk Management.

Hoffmann-La Roche, Inc. Presentations

Introduction

MS. WAUGH: Good morning.

[Slide]

I am Joanna Waugh, from the Regulatory Affairs Department at Hoffmann-La Roche, Nutley, New Jersey. Thank you to the FDA and the committee for giving us the opportunity to present today.

[Slide]

What I would like to do first is to just

give you an overview of the framework of our presentation today. Having heard the FDA presentation, there is some overlap with our presentation so we will go fairly rapidly through some of the areas where there is duplication.

Following myself, Dr. Martin Huber will provide a brief overview of the risk/benefit profile for isotretinoin. I will then briefly summarize a regulatory overview, focusing on risk management milestones for Accutane since its launch in the U.S. in 1982. Dr. Susan Ackermann Shiff will then provide an overview of the S.M.A.R.T. program, comprising a description of what that program entails, as well as an assessment of some of the data with particular reference to metrics which were predetermined in agreement with FDA. Dr. Martin Huber will then review the pregnancy data from the S.M.A.R.T. program and move on to discuss our recommendations for program modification.

[Slide]

In addition to the team of presenters

which are listed on the left-hand side of this slide, Roche does also have available, for responding to questions in the question and answer session, some additional colleagues, Miss Kay Bess from our Drug Safety Risk Management Department, Dr. Karen Blesch, from the same department, Miss Tammy Reilly, Vice President of Dermatology and Oncology, and Dr. Susan Sacks, from the Drug Safety Risk Management Department.

[Slide]

Additionally, we have available the following outside experts for responding to questions, Dr. Diane Berson, from Cornell University; Dr. Judith Jones, from the Degge Group; and Dr. Victor Strecher, from the University of Michigan School of Public Health.

[Slide]

As this slide shows and was referred to by the FDA in their presentation, the S.M.A.R.T. risk management program was approved in 2001 and it was subsequently implemented early in 2002. Since 2002 generic isotretinoin has also been available on the

U.S. marketplace and this slide shows the respective manufacturers' products and risk management programs, which are all equivalent to the Accutane S.M.A.R.T. risk management program.

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The conditions for the approval of the S.M.A.R.T. risk management program included the requirement to develop a backup program for a mandatory registry, as well as the understanding that a follow-up advisory committee would be convened when more data was available to discuss the effectiveness of the program, which is why we are here today. When more data was available, Roche evaluated that data and developed a specific proposal for program enhancement based on the data we saw emerging.

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In December of 2003, the FDA, Roche and the generic companies reviewed the data across our respective risk management programs. Roche and the generic companies subsequently worked together on recommendations for program modification. All

companies agree on the need for one single program and the recommendation that you will hear put forward today is generally agreed to by all the companies. The details of the implementation require some further refinement and discussion and we look forward to the discussion from the advisory committee today on the proposal that we will put forward to you.

I will now hand over to Dr. Martin Huber.

Benefit/Risk

DR. HUBER: Good morning.

[Slide]

What I would like to briefly review for you is the benefit/risk. As a first step in any risk management approach there needs to be an assessment of both the benefit and the risk that we are addressing.

[Slide]

Just to remind you, isotretinoin is indicated for severe recalcitrant nodular acne. It is indicated only for patients who are unresponsive to conventional therapy, including systemic

antibiotics. Finally, it is indicated only for those females who are not pregnant and agree to not become pregnant.

[Slide]

The medical need for isotretinoin is because it is a serious disease with profound consequences. Inadequately treated severe recalcitrant nodular acne can lead to disfiguring scarring. Fortunately, it is a uniquely efficacious therapy for this condition and there are currently no alternative therapies for these patients.

[Slide]

To briefly remind you, this is the concern. Inadequately treated SRNA can lead to disfiguring scarring which is life-long.

[Slide]

However, there is a specific challenge for isotretinoin, as has been indicated by the previous speakers. Isotretinoin is known to be a human teratogen. The majority of the female patients who use this drug are of childbearing potential.

Therefore, pregnancy prevention measures, including proactive risk management, are essential. But the specific challenge of this program is that we must change the behavior of patients in order to have them comply better with these risk management programs.

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The public health goals, as previously stated, remain the same. Our vision is that no woman who is pregnant should receive isotretinoin therapy; no woman should become pregnant during or for one month after receiving isotretinoin therapy.

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I will now turn it over to Miss Waugh who will review the regulatory history and the risk management program to date.

Regulatory Overview

[Slide]

MS. WAUGH: The teratogenic risk of Accutane has been known since the approval of the drug in 1982 in the U.S. Because of this known risk, we have taken a variety of risk management

steps throughout the product life cycle with the aim of reducing pregnancies as far as possible. The proposed program that you will hear today includes risk management enhancements in response to data that we have seen in the S.M.A.R.T. risk management program.

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This slide provides an overview of some examples of steps Roche has taken throughout the product life cycle to minimize pregnancies. Since product launch in 1982, the product had a pregnancy category X, i.e., it was contraindicated in pregnant women. In 1984 a black box warning was introduced to increase the prominence of warnings surrounding pregnancy.

In 1988 the Pregnancy Prevention Program was introduced which FDA alluded to in the earlier presentation. This was the first risk management program of its kind which used mechanisms over and above labeling as tools for risk management. Some components of the Pregnancy Prevention Program are listed on this slide and I will just go through

them briefly, the requirement for two forms of contraception to be used simultaneously for one month before, during and after Accutane treatment. Additionally, the requirement for negative monthly pregnancy testing; the addition of an "avoid pregnancy" symbol in the packaging. Educational materials were introduced regarding contraceptives and pregnancy avoidance, and a female informed consent form was introduced.

Further evaluation tools to assess the effectiveness of this program were introduced which included the Accutane survey. This survey was developed by the Slone Epidemiology Center at Boston University and provided information about women's understanding of the risk issues related to teratogenicity, as well as some information about the pregnancy rate based on the number of women enrolled in the survey.

[Slide]

in 1990 we added information to the U.S. product information concerning a description of birth defects that could occur, as well as a

recommendation that prescribing should be limited to a one-month supply.

In 1994 the patient informed consent form was updated to include additional requirements. In May of 2000, amongst additional requirements, one of the requirements was to have two negative pregnancy tests prior to the initial prescription.

In September of 2000, as has been mentioned earlier, an advisory committee was convened which discussed pregnancy prevention. I will come back to that in a little bit more detail later. Subsequent to that advisory committee, Roche worked in collaboration with the FDA to determine how best to implement their recommendations. The result of these discussions was the ultimate approval for the S.M.A.R.T. risk management program in October, 2001.

[Slide]

As I mentioned, the 2000 advisory committee discussed pregnancy prevention. The recommendations from that advisory committee, as mentioned by the FDA, included the recommendation

for the introduction of patient and prescriber registry. In subsequent discussions with the agency, Roche put forward various proposals which included mandatory patient and prescriber registration. In discussions with the agency about the best way to implement these recommendations and in view of some of the issues that FDA alluded to earlier, Roche and FDA agreed that the critical issue was to link a negative pregnancy test with each prescription and dispensing of Accutane.

[Slide]

The S.M.A.R.T. program introduced a link between dispensing and negative pregnancy testing via the Accutane qualification sticker. Additionally, the S.M.A.R.T. program included enhanced education, enhanced informed consent, and the requirement for prescribers who wish to prescribe Accutane to be registered into a database.

[Slide]

Dr. Susan Ackermann Shiff will now provide more details about the S.M.A.R.T. program.

Overview of the S.M.A.R.T. Program

DR. ACKERMANN SHIFF: Thank you.

[Slide]

What I would now like to briefly do is overview the S.M.A.R.T. program or the System to Manage Accutane-Related Teratogenicity. The program was developed with and approved by the FDA, and went into effect on April 10 of 2002.

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This high level overview slide provides two important features, first that the registered, qualified physician, the qualified patient and the pharmacist work together in the dispensing of the product. Second, the qualification sticker is the one area where the negative pregnancy test and the dispensing of the product is linked.

[Slide]

Different from the Pregnancy Prevention Program, all prescribers must be enrolled in the program in order to prescribe the product. A prescriber will read the guide to best practices, sign a letter of understanding and receive the

qualification stickers.

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When the prescriber signs the letter of understanding they attest to the fact that they know the risk and severity of fetal injury and birth defects; that they know how to diagnose and treat various forms of acne; that they know the risk factors of unplanned pregnancy and they will properly follow the S.M.A.R.T. procedures. In this case, it includes education, pregnancy testing, contraception, informed consent and offering of the Accutane survey.

[Slide]

Once the prescriber has been registered within the system, they can educate the patient on the appropriate use of the product. The "Be Smart, Be Safe, Be Sure" educational brochure that is shown on this slide contains elements of education about the product; contraceptive information; the two informed consents, the all-patient informed consent and the female patient informed consent; an enrollment card for the Accutane survey; and

educational reinforcement. The purpose of this brochure is that it be used at the initial office visit and all subsequent office visits.

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As Roche understands that patients learn in different ways, we have also provided a variety of other educational materials. There are story boards in both English and Spanish and two educational videos, one about contraception and one about the risks of unplanned pregnancy. There are two 1-800 lines, one for Accutane information and one for contraception. In addition, there is an "avoid" blister pack pregnancy symbol and a medication guide that is now packaged in the blister pack that has information about the product and is patient friendly.

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There is also a patient education brochure for men that contains product information, informed consent and educational reinforcement.

[Slide]

The qualification sticker signifies that

there is a qualification date that, in this case, is the date of the last negative pregnancy test, not the date that the pregnancy test was received. The pharmacist must dispense within seven days of the qualification date and can't dispense more than a 30-day supply. No refills are allowed. Both males and females have a qualification sticker attached to their prescription.

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The qualification criteria or what the sticker represents on actual presentation is that the female patient has had the negative pregnancy testing, two at the start of therapy and one every month during therapy. In addition, she has selected and committed to use two safe and effective forms of contraception. She has signed all-patient informed consent and the female informed consent, and has been offered the opportunity to participate in the Accutane survey and knows of its importance.

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Again, the qualification sticker is the

actual sticker that links the dispensing of the product with the negative pregnancy test. The pharmacist will allow no more than a 30-day supply; will dispense within seven days of the qualification date or the date of the last negative pregnancy test; and no refills are allowed. In addition, no telephone, computerized or mail order prescriptions are allowed. The pharmacist also has the opportunity to verify that the physician has been entered into the system by calling a 1-800 number.

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What I would like to do now is to review the data from S.M.A.R.T. year one, or April 1 of 2002 through March 31, 2003. In some cases I will be comparing these data to the year previous to S.M.A.R.T. or the last year of the Pregnancy Prevention Program which is April 1, 2001 through March 31, 2002.

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We used three specific data sources to evaluate the S.M.A.R.T. program in year one. The

first is the prescription compliance survey; the second, the Accutane survey; and, three, pregnancy reports. I will be reviewing the first two data sources and Dr. Huber will be reviewing the pregnancy reports in addition to the corresponding failure analyses.

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The prescription compliance survey is a quarterly survey of a random sample of pharmacies pertaining to the use and completion of the qualification stickers. In addition, Roche conducted a quarterly audit of anonymous Accutane prescriptions from a random sample of these participating pharmacies. While I will not be discussing the quarterly audit, what I can say is that the results are consistent with the quarterly sample of the random sample of pharmacies.

[Slide]

There is one major objective of the prescription compliance survey, that is, to assess prescribers' and dispensing pharmacists' compliance with the appropriate use of the qualification

sticker.

[Slide]

During our discussions with the FDA, we had decided on two specific sets of metrics with regard to the prescription compliance survey. The first is that by the end of S.M.A.R.T. year one 90 percent of all physicians would use the qualification stickers. The secondary metrics included that 90 percent of all physicians would completely and correctly fill out the stickers, and that 90 percent of all prescriptions would be dispensed with a medication guide. In October of 2002 Roche started packaging the medication guides within the blister packs so the secondary metric is no longer applicable.

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The results of the prescription compliance survey are as follows: Over the six waves of the survey an average of 97 percent of all prescriptions had a qualification sticker affixed. Of those, 96 percent were correctly or completely completed. There were no differences between the

survey waves and there were no differences between the age of patient, the gender of patient, the location of the dispensing of the prescription or the payer type. In conclusion, we have met and exceeded our metrics for stickers and the mechanics of the stickers are working well. [Slide]

Now I would like to review some of the high-level results from the Accutane survey.

[Slide]

As Ms. Waugh noted previously, the Accutane survey was developed by Slone Epidemiology Center of the Boston University School of Public Health. It was initially implemented with the Pregnancy Prevention Program in 1989 and, to date, Roche has had two vendors for the survey. From 1989 to the presentation of these data, Slone Epidemiology Center was our primary research organization. In October, 2002 we switched research organizations to SI International and the Degge Group.

While I won't go into detail about the methodology of the survey, and I know that Dr.

Mitchell is presenting later, what I do want to note is that there are two specific arms within the Accutane survey, the Accutane after treatment arm and the during and after treatment arm. The presentation of these data deal only with the during and after treatment arm. In addition, I would also like to note that the research organization SI/Degge did implement the questionnaire that was modified to include components of S.M.A.R.T.

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There are four specific objectives of the Accutane survey. It was a voluntary survey to determine female patient awareness of the teratogenic risks of Accutane. In addition, it is used to measure compliance with key components of S.M.A.R.T., in this case informed consent, the medication guide, pregnancy testing, contraceptive use and the qualification sticker. Historically, we have used data from the Slone Epidemiology Center to calculate a rate of pregnancy among female Accutane users and to identify risk factors

that occur with pregnancy.

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Again, during our discussions with the FDA we had agreed upon a variety of primary and secondary metrics, the primary metric being that 60 percent of all women would enroll in the Accutane survey by the end of S.M.A.R.T. year one. We have several data specific secondary metrics including female patient representativeness; recall of qualification sticker; recall of pregnancy test; medication guide; the use of two forms of safe and effective forms of contraception; and enrollment in the Accutane survey via the prescriber's office, from the blister pack or by calling a toll-free number.

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Before I go on to specific review of the data, I would like to give you a high-level overview of our findings. We were successful in increasing enrollment in the Accutane survey by approximately 10 percentage points but missed the 60 percent metric.

We found that females recalled the use of the qualification sticker and that percentage was almost 100 percent. In addition, almost 100 percent of all women knew the risks of taking Accutane while pregnant and were told to avoid pregnancy during Accutane. However, they did not receive the pregnancy testing or were not using contraception according to the package insert.

With regard to the enrollment rate, we calculated an enrollment rate by dividing the number of enrollees by the number of new patient female starts. The result for the first year of S.M.A.R.T. is 28.2 percent of enrollment of all female Accutane users, which was up from 17 percent in pre-S.M.A.R.T. year one. While, again, we increased the enrollment rate, we did not succeed in meeting the 60 percent metric.

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However, when you look at the method of enrollment, we were very successful in shifting the method of enrollment from the blister pack to the physician's office. Again, if you remember, the

enrollment card is within the "Be Smart, Be Safe, Be sure" educational brochure and we see this as a marker that education was occurring within the physician's office.

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When we asked females at the start of therapy what might Accutane do if it is taken during pregnancy, and did your doctor tell you the importance of avoiding pregnancy while on Accutane, almost 100 percent of all women indicated that it causes birth defects and that their physician told them the importance of avoiding pregnancy while on Accutane.

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However, when we look at two important components of the S.M.A.R.T. program, pregnancy testing and contraceptive compliance, we found that only 64 percent of all women at the start of treatment indicated that they had received two pregnancy tests. We were successful in reducing the women that reported no pregnancy tests from 18 percent to approximately 9 percent, but a large

proportion of women did not receive the pregnancy testing according to the package insert.

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When we looked at the risk category at the start of treatment, we found that 50 percent of all women were not sexually active but 44 percent of all women reported some sort of sexual activity.

[Slide]

When we looked at sexual activity by use of two forms of contraception, we found that 41 percent of these women indicated that they were not using two safe and effective forms of contraception at the start of their treatment.

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When we looked at non-compliance with contraception by age, we noticed that females 12-19 reported the highest percent of not sexual activity. However, women 20-29, 30-39 and 40-44 who were sexually active reported high levels of not using two forms of contraception, 20 percent, 35 percent and 40 percent respectively.

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We noted previously from the prescription compliance survey that a large percentage of prescriptions had the sticker affixed. In this case, the percentage is similar, 97 percent of all women indicated that a qualification sticker was affixed to their prescription. However, when we asked them about baseline pregnancy testing, receipt of two or more pregnancy tests and sexual activity by using two safe and effective forms of contraception, the percentages were no different between those women who reported a qualification sticker affixed to their prescription and those women who did not. In fact, when we look at the 22 cases of pregnancy, 20 of those cases of pregnancy occurred in women who claimed to have a qualification sticker attached to their prescription.

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Further, when we looked at these same data during treatment, 21 percent of all women during treatment indicated that they had not received a pregnancy test. Only 63 percent of these women

indicated that they had received two or more pregnancy tests. Again, during this time in the course of their treatment they should have received at least three pregnancy tests.

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Forty percent of all women indicated they were sexually active during treatment. However, 52 percent of these women indicated that during treatment they were not using two safe and effective forms of contraception as outlined in the S.M.A.R.T. materials.

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However again, we found that almost 100 percent of all women said that they had seen a qualification sticker on their prescription during the course of their treatment.

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In summary, we believe we were successful in increasing the enrollment of the Accutane survey by 10 percentage points, however, we did not meet the 60 percent metric set out. We increased the proportion of patients enrolling vis-a-vis the

prescriber's office. For us, that was an indication that education is occurring within the prescriber's office. And, we believe that the mechanics of the sticker are working well.

[Slide]

In addition, from the percentages in the Accutane survey, women do understand the need to avoid pregnancy and the consequences of becoming pregnant while on Accutane. However, there was incomplete compliance with both pregnancy testing and with contraception. In fact, we found little relationship between the qualification sticker, pregnancy testing and contraception.

[Slide]

Dr. Huber?

Evaluation of S.M.A.R.T. Program

[Slide]

DR. HUBER: I would now like to briefly review the pregnancy case reports that we have received at Roche and put them in perspective--as Dr. Crawford was asking earlier, the case value analysis basically.

[Slide]

First, I would like to go briefly through the methodology. These reports come from multiple sources. These are exposed pregnancies that are reported via either of the vendors for the Accutane survey or via spontaneous reports from healthcare professionals or consumers.

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In order to compare the pregnancy numbers from S.M.A.R.T. and the pre-S.M.A.R.T. year we set up the following metrics so that the numbers would be somewhat comparable. What we refer to here as pre-S.M.A.R.T. is that treatment was started so isotretinoin or Accutane was started between April 1, 2001 to March 31, 2002. But, because there are delays in receiving some of these reports, we allowed that the report was received by August 15, 2002. The S.M.A.R.T. data is essentially these same definitions but one year later.

The other issue we have to deal with in the analysis of these data is that there are numerous reports that come in, in which there is no

therapy date stated on the report. We don't know when the therapy started. In fact, when you review these, in some of these it is fairly explicit that the therapy was years ago. So, we include this category of therapy start dates unknown and, because we don't have a therapy start date, we assign them to the period in which the report was received.

[Slide]

To give some context to these reports--there have been numerous questions about rates, etc.--what I would like to do is remind you of the overall use of the product. First, the majority of these reports are from spontaneous reporting sources, not from the survey. Also, overall Accutane use has been declining since 2000. I would like to focus on the estimated number of females treated. This is female patients in total, not just childbearing, and this is Accutane. So, you see 278,000, 253,000, 218,000. I would like to note that generics were introduced in 2002. So, when you see 2003 here, the 128,000 reflects purely

the Accutane, not isotretinoin, data.

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These are the pregnancy case reports we have received according to the cut-offs I defined earlier. For pre-S.M.A.R.T. there was a total number of 150 pregnancies; for S.M.A.R.T., 183. If we focus on those in which there is a treatment initiation date known to occur in the period, it is essentially 94 and 94. Where the biggest increase has been is in this group of patients, these 89 with treatment initiation date unknown. I will go into a little more explanation of why we think this occurred in the next few slides.

[Slide]

We think it is unlikely that the true number of pregnancy case reports is a true increase. In other words, we don't believe it is possible that an increased educational program, with increased monitoring and with the qualification sticker actually led to more exposed pregnancies. Rather, as has been noted by several of the previous speakers, in a spontaneous

environment there is a percentage of reports that you receive and a percentage you don't know about. We believe that this is most likely what is occurring here and that with the first year of S.M.A.R.T. we have actually seen an increased proportion of reporting.

Why did that occur? Of note, there was increased awareness among physicians with S.M.A.R.T. There was also, as Dr. Ackermann noted, increased participation in the survey. Finally, there is increased education and awareness among patients.

[Slide]

To go through the details of these cases now, I will start with what is the source of these reports. We follow the convention of this in pre-S.M.A.R.T. with a known therapy start date; S.M.A.R.T. with a known therapy start date; this is pre-S.M.A.R.T. and S.M.A.R.T. with an unknown therapy start date cases. This bottom color here is those cases that came in via the Accutane survey from either vendor. The green is direct to Roche

from a healthcare professional. This orange is direct to Roche from consumers or others.

What you see here is that the most substantial increase in number of pregnancy reports is this 10 to 33 in association with the Accutane survey. Also consistent with increased awareness from consumers, while we didn't see an increase here, what we did see was a substantial increase from 19 to 30 of these cases coming to Roche from consumers that had this unknown therapy start date.

[Slide]

When we start looking at this, as has been noted, there are really two issues here. There are those patients who are pregnant prior to starting Accutane therapy and then those patients who become pregnant on Accutane therapy. These data try to break this down. We looked specifically at the patients who were pregnant prior to starting Accutane therapy. For the pre-S.M.A.R.T., of the 150 pregnancies, 28 or 19 percent occurred in the pre-S.M.A.R.T. year; S.M.A.R.T. year one, 24 of 183 or 13 percent occurred prior starting Accutane

therapy. If we look at the number that became pregnant while on Accutane therapy, 51 percent, 41 percent with approximately the same numbers. Patients becoming pregnant within 30 days after stopping, 44 or 29 percent, 58 and 31 percent. The biggest increase is in this unknown category but, as I stated earlier, this does include a large number of cases that had unknown treatment initiation and they also had unknown pregnancy date.

[Slide]

Looking at the demographics of these patients, these are the same patients, 153 S.M.A.R.T., 183 S.M.A.R.T., broken down by age. Of note, when you look at the 16-19 group or from 19-29, 12-15 percent. What is interesting is the age group 20-29 declined from 41 percent to 24 percent but please note that 20-29 remains the largest category of patients, and 30-39 is essentially similar, 16 and almost 15 percent and once again a large number of unknown in S.M.A.R.T. year one. The mean or median did not shift

significantly.

[Slide]

Now coming to why are these people getting pregnant, we looked for evidence of educational and compliance understanding of patients. These are not a linkage of survey data to these case reports. Rather, this information is gathered as part of our follow-up procedure for the pregnancy case reports.

The green is yes, the orange is no and the light, pale color here is unknown. What I would like to do is focus on the signed female informed consent, received a spiral notebook and enrolled in the Accutane survey. The axis here is the number of pregnancy case reports that qualified for each category. These are now the S.M.A.R.T. year one cases only.

What we see here is that only three patients stated no to recall of a signed female informed consent. Only five patients stated no to receiving a spiral notebook and this is in the group that is our worst outcome group in that they got exposed pregnancy, and seven said no to

enrolling in the survey. So, of those that answered, the interpretation of the data is they are getting the educational materials. This is also consistent with what Dr. Ackermann talked about in the survey where 99 percent of the patients know they are not supposed to get pregnant. They do receive the educational materials.

[Slide]

The problem, as we see it, is linking it to compliance with the behaviors in the program. Using the same format, this is once again S.M.A.R.T. year one, the number of pregnancy case reports are on this axis, two baseline pregnancy tests, monthly follow-up pregnancy tests, used two forms of contraception, and was the qualification sticker attached.

I will start on the right first and 58 versus zero recalled the qualification sticker and this is among the patients who became pregnant. What is most disturbing is that 16 said no to the question of baseline pregnancy tests; 8 said no to

monthly follow-up pregnancy tests; and 6 said no to using two 2 forms of contraception. So, what we detect in this data is a pattern of failure to comply with the educational materials that they received.

[Slide]

I would like to review briefly the methods of contraception in these cases. Now we are pre-S.M.A.R.T. and S.M.A.R.T. and these were focusing on the 94 with the known start date in both groups. Of note, 10 were pre-S.M.A.R.T.; 11 of S.M.A.R.T. were using abstinence as a primary method of contraception. Of note, of these 11 cases that reported abstinence, 4 did report additionally using condoms.

For the two forms of contraception, 17 pre-S.M.A.R.T., which increased dramatically to 30 in the S.M.A.R.T. reports, reported using two forms, one primary and one secondary. No one reported in either year using two forms of secondary contraception. With regards to one form of primary, 18 and 18; one form secondary, 14 and

11. Unknown declined from 27 to 19.

[Slide]

To put these numbers in perspective I am going to use some data from the Accutane survey. Dr. Mitchell will talk in more detail about these later. But this is the one set of data we have in which we have a numerator--the number of pregnancies via the survey, and a denominator--the number of patients who enrolled in the survey. However, this applies only to the Slone Accutane survey participants. We have not calculated this rate for year one of S.M.A.R.T. in the SI because there is an issue with the follow-up necessary to get the patients in and sufficient follow-up is not there yet.

The other thing is that pregnancy rates get reported in multiple ways. So, you are going to see some numbers potentially through the course of this day kind of flying around. I would like to show you two ways to try and help you understand. One approach has used Accutane exposed pregnancies per 1,000 of the 140-day Accutane treatment

courses. Given that the normal treatment course is 140 days, one approach has been to analyze the exposed pregnancies by treatment courses. So, when you see the 140-day treatment course, this is what we are referring to. The other way which you will see used is the number of Accutane exposed pregnancies per 1,000 patients per year.

[Slide]

On this slide we are looking at these data by both methods. On the left vertical axis here, this is the number per treatment courses. This is when we refer to the 140; zero on the bottom, 4 on the top. This is the blue line, over time within the survey and enrollment date year 1989 to 2002 and we decline from 4 down to a rate of about 2.9.

If you take these same data and do it by number of pregnancies per 1,000 patients per year you go from this axis, over here, around 10 to around--sorry, that is 2.9; the other one was 1.2. I apologize.

The basic message is that we have seen a decline in the rate within the survey as we have

gone through a series of risk management steps. That is important to remember when we discuss next steps. There has been some progress and I want to make sure we don't lose that in our next activities.

[Slide]

So, what do we conclude on the basis of these pregnancy data? We believe that there were moderate decreases in the number of women who initiated Accutane therapy while pregnant. Those are those 19 percent declining to 13 percent, basically those women who were pregnant before S.M.A.R.T. We think this reflects a slight improved intervention with S.M.A.R.T.

However, there was a relative increase in the number of pregnancies reported. We believe this is likely due to increased awareness. This, in fact, probably reflects an improved assessment. You are getting more data. But the fundamental problem is that pregnancy is associated with incomplete compliance with risk management parameters.

[Slide]

The goal of the enhanced program remains the same as we started with initially. No woman who is pregnant should receive isotretinoin therapy. Our specific proposal, which I will outline for you, is that we need to further enhance the link of a negative pregnancy test to dispensing of the product.

With regards to the second public health goal, no woman should become pregnant during isotretinoin therapy, we believe this is best accomplished by attempts to enhance patient compliance with a behavior component, more specifically, increased use of contraceptives, and we will also cover that in our new proposal.

[Slide]

Now for our recommendations, our proposal is for a single information system that provides a verifiable link between a registered physician with the results of laboratory conducted pregnancy test, a registered patient including patient interaction with the educational and risk management evaluation

component of the system, and a registered pharmacy with a link to a product dispensed.

[Slide]

I will now try to walk you through the path for females of childbearing potential. After I have completed this I will come back and walk through what we propose for non-childbearing potential and males.

[Slide]

First, a potential candidate for Accutane is identified. They see a registered physician. The physician determines if a patient is an appropriate patient. They determine if they are of childbearing potential. They perform a screening pregnancy test. This can be done in the office. They educate the patient, provide them materials and they provide informed consent. In the current proposal the majority of these materials are generally consistent with what is currently available in the S.M.A.R.T. program. The difference is that the physician then enters this information and confirmation into a central

registry. The registry, in return, will give the physician a unique patient identifier number for that patient.

[Slide]

The patient then will leave the office and, using their unique patient identification number, interact with the system. What they will be doing is interacting with educational and risk management components. Potentially this is interactive voice recognition. There are alternative approaches we can do, but the focus is on reinforcement of compliance with the two forms of contraception that they have originally been educated on by the provider.

[Slide]

There are two visits involved for a woman of childbearing potential. She comes back to the dermatologist's office, consistent with our current approach, and then will have a laboratory pregnancy test obtained. What we were recommending here, because of the concerns about the pregnancy testing deficiencies in the current approach, is that all

women have a laboratory pregnancy test and that the results of that laboratory test be entered into the system.

At this visit there is further education of the patient with a focus on the reinforcement of compliance with two forms of contraception. At this time the patient receives the prescription with the qualification sticker with patient ID.

[Slide]

The patient then goes to a registered pharmacy that verifies the qualification sticker and verifies the treatment is authorized. They do this by calling into the registry and basically receiving a yes or no, the patient is qualified or not. If the patient is not qualified, which means that they have either not bee appropriately registered, something has happened on their interaction with the educational, or there is not a negative pregnancy test in the system that falls within the prescribed dates, that patient is told no and is asked to contact the physician. If it is authorized and they provide product information,

obtain a confirmation number, the medication guide is dispensed, they dispense the medication.

[Slide]

The patient will continue to receive only a 30-day supply, as noted here. Thirty days later they will loop back into this system in which they will do further interaction with the educational risk management component, have a laboratory confirmed test, further education and receive the prescription for the next 30 days.

[Slide]

For males and females of non-childbearing potential it is essentially the same but the requirement for the pregnancy test is out of the system. It makes it a little simpler.

You have the same determinant qualification. You educate patients generally on the product; the informed consent. There is a male informed consent as well. Part of the education here is focused on not sharing of the pills with a female partner. The patient receives the prescription with qualification sticker. The

patient is registered and receives an ID. The reason for putting them into the system is that in order to control the dispensing it is important that every patient go through the same process and there not be two parallel dispensing routes for males and females. The registered pharmacist does the same process. Once again, it is a 30-day renewal.

[Slide]

In addition to this, there will be a centralized pregnancy registry which will provide a system for reporting, confirming and follow-up of all pregnancies in a uniform fashion. This should enhance our failure analysis efforts and it will facilitate calculation of a risk-exposed pregnancy rate.

[Slide]

How has this evolved from our current S.M.A.R.T. program? This is PPP, S.M.A.R.T., and this is the proposed new program. There is now registration of patients, registration of pharmacies. More important than the actual

registration act itself is what this allows us to do. What it allows is a stronger check on the prescriber because there is now this registration into the system. It allows a hard link of the patient's interaction with the system on education and risk management to dispensing. If they don't interact with the system appropriately they cannot get the product. There is also a hard link to a laboratory pregnancy test which we see as an enhancement. This increases your ability to audit; potentially gives you more opportunities for interaction with regards to contraceptives and, finally, we will have a centralized pregnancy reporting process.

[Slide]

When we consider this we see benefits and challenges. From a benefit point of view, we see two important improvements. It improves the link between dispensing and compliance with both pregnancy testing and pregnancy prevention activities. The interaction with the system on the educational and risk management components of this

is important to try to address the compliance with the necessary behavior regarding pregnancy prevention.

This should also improve data quality reporting. We will now have 100 percent of the patients in the system and gathering data on these patients.

It also provides opportunities for real-time patient qualification assessment linked to dispensing. The questions are asked as part of the loop on compliance with various behaviors prior to dispensing.

Because this data will now be gathered on all patients on an ongoing basis, it should provide us opportunities to enhance risk management evaluation activities. Various questions exist on what are the risk factors for failure. This should allow us to better address these on an ongoing basis.

What are the challenges? One concern is that we are now interfering with the primary relationship between the prescriber and the

patient. This is still the primary basis for prescribing of medications. What we see this system as is an enhancement of that relationship. We will certainly, however, have to remain cautious with regards to privacy issues in this setting.

The other potential concern is the size of this program. There are other risk management programs for pregnancy currently out there but the logistics, the size and scope of this is substantially larger than the other programs. That, in and of itself, is not a major issue but if any of these other issues becomes a barrier to the patient's access to the product, if we make it so burdensome that the patients choose not to go with this mechanism, the concern is that patients will pursue alternative sourcing. If patients move dramatically to alternative sourcing we will undermine the overall public health goal.

[Slide]

In conclusion, we propose the program enhancements that establish a verifiable link between a prescriber, a patient, a pharmacy, the

negative laboratory-conducted test, the patient interaction with the educational and risk management system and the product dispensed.

[Slide]

This should reduce the number of women who are pregnant when they receive their initial prescription. Also, the educational component would reduce the number of women who become pregnant during isotretinoin therapy. It will also enhance pregnancy detection and follow-up.

There is one word of caution here. If you enhance your assessment, increase the proportion that you find because 100 percent of the patients are in the system, the number of pregnancies reported--not that occur but that are reported--may initially increase.

[Slide]

I would like to put this now into perspective of the FDA's risk management model to kind of get some guidance on where we are in this process. We have identified the issues. We see it as two major issues for this committee today, those

patients who are pregnant before receiving an isotretinoin prescription and those patients who become pregnant during they.

We assessed the risks and benefits. We have gone through the benefit of this product. It is an essential product for which there is not an alternative therapy. However, there is a risk which is specific to a subpopulation of the patients.

We have identified and analyzed options. We have proposed to you today our recommended strategy. Assuming that is implemented, then we will need to evaluate the results.

Today we sit here, in this middle circle, engaging you and your advice on how we can do this in a better fashion. I would like to thank you for your time and attention. If I understand it correctly, we are going to do questions after the other manufacturers. Thank you.

DR. GROSS: Thank you very much. I am going to pass the chair now to Dr. Stephanie Crawford. I have to step out for about an hour.

She will introduce the generic firms' presentations. Thank you.

DR. CRAWFORD: Thank you. Dr. Gross seems to think I am going to relinquish the chair back to him when he returns.

[Laughter]

At this point in the program, we welcome the opportunity to hear from the generic firms' presentations and the three speakers will be Dr. Frank Sisto, Dr. Allen Mitchell and Mr. Robert Pollock.

Generic Firms Presentation

Isotretinoin Risk Management Program, Background Information

MR. SISTO: Good morning.

[Slide]

My name is Frank Sisto and I am Vice President of Regulatory Affairs for Mylan Laboratories, which is one of the companies that are currently involved in the marketing of generic isotretinoin in capsules.

The presentation which we have put

together for you today from the generic companies involves three parts. The first part, which I will give, provides some background information regarding the first year of marketing for the generic isotretinoin products, including identification of the pregnancy cases that have been reported to the various generic companies which we have then subsequently reported to FDA.

The second presentation will be given by Dr. Allen Mitchell, from the Slone Epidemiology Center at Boston University. Dr. Mitchell will provide information with regards to the voluntary isotretinoin survey that has been conducted for the various generic companies from December, 2002 when the first generic product came on the market, through December, 2003.

The third part of our presentation will be given on behalf of all the generic companies by Mr. Robert Pollock. Mr. Pollock will present three of the elements of a proposed enhanced risk management program for which we are interested in getting some additional input from the committee members.

[Slide]

With regard to my presentation, I would like to first reiterate the fact that there are currently three generic isotretinoin products approved and marketed which are therapeutic equivalents to Accutane. Amnesteem, which was approved under an ANDA from Genpharm and is marketed by Mylan and Bertek Pharmaceuticals, was approved in November of 2002 and was first marketed in December of 2002, a little over a year ago. Sotret, which is the generic isotretinoin capsule product from Ranbaxy Pharmaceuticals, was first marketed in March of 2003, and Claravis, which is the generic isotretinoin capsule product from Barr Laboratories, was first marketed in May of last year.

It is also important to note--and you have heard this a couple of times today in presentations--that although the risk management programs for each of these products has a different name, and that was an issue which had to do with trade names and copyrights which is the reason for

that, all of these risk management programs are equivalent and substitutable or interchangeable and they are equivalent to the S.M.A.R.T. risk management program that was approved by FDA and implemented by Hoffmann-La Roche in early 2002.

As the risk management program is considered by FDA to be part of labeling, it is required that these programs be the same as for the Accutane or innovator product, and that FDA find these components acceptable as a condition of approval for the generic products.

[Slide]

Since I am going to be talking about the number of pregnancies that have been reported to the various generic companies and subsequently reported to FDA, I wanted to put that in perspective by providing a little information with regards to the prescriptions dispensed by each of the generic companies since the marketing has begun.

Going back to December of 2002, which was the first month when the first generic product,

which is Amnesteem, came on the market, there are approximately 104,000 prescriptions dispensed per month. This went down to about 91,000 in the time frame around August of '03 and in December of '03 when all three generic products were on the market the total number of prescriptions was around 117,000. Of those prescriptions in December of 2003 for Accutane from Hoffmann-La Roche and Amnesteem from Bertek Pharmaceuticals, there were about 43,000 or 45,000 prescriptions a month. For the Claravis product from Barr, there were about 17,000 prescriptions per month and for the Sotret product from Ranbaxy there were about 8,500 prescriptions per month.

[Slide]

In terms of market share, it is important to see that within the first 4 months of marketing of the Amnesteem product, the first generic product that was approved in December of '02, Amnesteem had acquired about 42 percent of the prescriptions in April of '03 and at the end of December of '03 this number had increased--well, 60 percent of the total

prescriptions in December of '03 were dispensed for the generic isotretinoin products. Of that, a little under 40 percent was for Amnesteem, about 14 percent was the Claravis product and about 8 percent was the Sotret product from Ranbaxy.

[Slide]

Just going back, about two and a half years prior to any generic product being on the market, I put this slide in here just to show that there has been somewhat of a decrease in the overall number of prescriptions over time. If you go back to April of '02, there were approximately 170,000 prescriptions per month at that time and Accutane was the product that was on the market. There were some enhancements to the program during the months that followed and that may have, in part, caused some of the difference in prescribing habits and some of the decrease that was seen in the number of prescriptions dispensed on a monthly basis.

In January of '02 the S.M.A.R.T. program was implemented and, in April of '02, that program

became mandatory. Again, these enhancements may have also affected in some way the prescribing habits for isotretinoin and caused somewhat of a decrease in the overall prescriptions per month. As previously reported, when all the generics were on the market at the end of December of '03 the prescriptions were approximately 113,000 per month.

[Slide]

Now, with regards to the number of pregnancies that have been reported to the generic companies, which we have subsequently reported to the FDA, there has been a total of 19 pregnancies reported since the first generic came on the market in December of '02 through February 5, 2004. Of these, 18 have been reported through Bertek Pharmaceuticals, the Genpharm Amnesteem product. One has been reported by Barr Laboratories for the Claravis product and zero have been reported for Ranbaxy. Of the 18 that were reported by Genpharm, 9 of those were captured in the Accutane survey which Slone is conducting and 9 were reported directly to the company.

[Slide]

With regards to the sorts of reports, as indicated, nine of those were reported through the Slone survey. Nine had a known therapy start date. Three were reported directly to the company by healthcare professionals. They also had known therapy start dates. The six that were reported directly to the company either by consumers or others had a known therapy start date, and there was one reported that did not have a known therapy start date.

[Slide]

With regards to the timing of exposure to isotretinoin therapy relative to pregnancy, it was found that three patients were pregnant when isotretinoin was started, when they started isotretinoin therapy. Six pregnancies occurred after the start of isotretinoin treatment. Five occurred within 30 days of the completion or stopping of isotretinoin treatment. Three occurred later than 30 days after completion or stopping of isotretinoin treatment. Although this is outside

of labeling and does not need to be reported, they were reported to us and we are just including them here for completeness. Also, two of the timing of exposures relative to the pregnancy were unknown.

[Slide]

With regards to the timing of exposure relative to pregnancy outcome, of the three patients that were pregnant when they started the isotretinoin treatment, one of those was lost to follow-up and two were terminated in therapeutic abortions. Of the six where pregnancy occurred after the start of treatment, one of those pregnancies is still ongoing; four ended in therapeutic abortion and one was unknown. Of the five pregnancies that occurred within 30 days of completion or stopping of isotretinoin treatment, three were lost to follow-up, one is ongoing and one ended in therapeutic abortion. Of the three that occurred greater than 30 days after completion or stopping of treatment, two are ongoing and one ended in therapeutic abortion and two are still unknown.

[Slide]

With regards to the pregnancy outcome versus offspring status, the only thing I really wanted to mention here is that there have been no deliveries to date so there is really nothing to report with regards to the offspring status.

[Slide]

With regards to the age group of the female patients for which pregnancies were reported, 2 were in the age range of 16-19; the majority, 11, were in the age range of 20-29; 3 were in the age range of 30-39 and 3 had unknown ages. Both the mean and median, which corroborates very well with the information provided by Hoffmann-La Roche, was around 25 years old and the range was 17-39 years.

[Slide]

The last thing that I wanted to mention has to do with the prescription compliance survey or the prescription audit that was conducted. Mylan/Bertek has conducted this audit, the only company to date since we have been on the market

the longest, and we conducted this audit in March of '03 and assessed isotretinoin prescriptions from April, 02 through December 31, '02.

What is important to note here is that in reality the only product that was on the market at that time was Accutane, except for the last two weeks of December. So, this really provides information with the risk management program and it provides a good baseline for the generics also. The objective of that program was to collect, analyze and validate the data pertaining to the dispensing of isotretinoin prescriptions under the current risk management program.

[Slide]

The primary endpoint for the survey or the audit was to determine the total number of stickered prescriptions, those prescriptions having a yellow qualification sticker, in the total pool of evaluable isotretinoin prescriptions. This survey was done for us by Express Script, Inc., or ESI.

The secondary endpoint was to determine

the total number of correctly completed isotretinoin stickered prescriptions in the total pool of evaluable prescriptions containing yellow stickers. Those were stickers where the male/female box was appropriately checked and which had the appropriate or specific date on them.

[Slide]

With regards to the results from the survey, 13,510 prescription-specific surveys, meaning information that was based on a review of actual prescriptions and not from memory representing 2,939 pharmacies, were returned. Of these, 96 percent reported that a yellow qualification sticker was present on the prescription, which was the primary objective of the survey. The audit and validation process with regards to this part of the survey revealed that 96 percent of the responses were correctly answered.

For the secondary objective, the survey revealed that a little over 97 percent of all prescription-specific surveys with a qualification date were filled out properly. The audit and

validation process for this part of the survey revealed that 96 percent of the responses were correctly answered. This very much corroborates or compares with the data which has been provided for the survey which was conducted for Hoffmann-La Roche.

With that, I would like to turn it over to Dr. Mitchell who will present information on the isotretinoin survey that he is conducting.

Isotretinoin Survey

DR. MITCHELL: Thank you.

[Slide]

It is a pleasure to be here this morning, as it has been over the past 14 years before FDA advisory committees. I do feel the necessity to make a disclosure, which is that I am a special government employee, which in English means that I am a consultant to the FDA, but that I am not engaged in any way in consultation with the FDA on these matters.

We will be presenting the results of the isotretinoin survey, by which I mean the survey

conducted for the generic manufacturers.

[Slide]

The survey extends the design, as noted before, that the Slone Epidemiology Center developed in 1989 for the Accutane survey under the sponsorship of Hoffmann-La Roche. We conducted the Accutane survey until July of 2003. Through that point we had enrolled approximately 592,000 women in that survey.

I should point out that the FDA, in the briefing materials, has reviewed some of the earlier survey findings, some of which we would concur with and others we would not. The schedule for this morning does not provide us an opportunity to respond to those critiques and we would welcome the opportunity to do so sometime during the day. If the committee would wish, we would do that briefly.

We have conducted the isotretinoin survey for the three generic sponsors since December of 2002 and we have enrolled through that period, to December 2003, 8,625 women. The objectives of the

isotretinoin survey, as was the case for the Accutane survey, are to assess compliance with pregnancy prevention efforts and specifically, as you have heard, the awareness of the teratogenic risk; patient and physician behaviors; pregnancy rates; pregnancy outcomes; and risk factors for pregnancy. I might add, and reinforce the point that has been made earlier, that when we say pregnancy rate we mean a meaningful pregnancy rate based on an identifiable and reliable denominator.

[Slide]

By way of background, I think it is useful to keep in mind that in the early phases when there was a single product we observed in our survey pregnancy rates in 1989 of approximately 4/1,000 courses of therapy and that rate, as has been noted, steadily declined, such that in the year in 2002 it was just a little bit over 1/1,000 courses.

I should also point out that we are in the midst now of conducting a risk factor analysis based on this very large sample of pre-S.M.A.R.T. data to see if we can identify any factors that

might predict women at risk of pregnancy that might not have been identified to date.

[Slide]

In 2001, in anticipation of S.M.A.R.T., the Slone Epidemiology Center modified the survey design and questionnaires with input both from Roche and the Food and Drug Administration. I should point out that a number of the questions that were included in the questionnaire were included at the request of FDA. Also, we provided the content of the revised questionnaire to Roche who, in turn, provided it to SI/Degge. The data that followed were collected for the generic sponsors, post-S.M.A.R.T., using the modified design and questionnaires.

[Slide]

Needless to say, there is a ramp-up period that is inherent in the marketing of different products. The generics were first introduced in December of '02 and we are covering essentially the one-year period until December 31 of '03. The number of enrollments received by quarters are

presented here. Obviously, it is increasing each quarter.

[Slide]

The method of enrollment by quarter is presented in this slide. As you can see, initially virtually all enrollments came from the enrollment form included in the medication package. That was a part of the design we created back in 1989. Only a small fraction at the outset, close to zero, came through doctor-generated enrollment forms. Those patterns began to shift over time and have continued to shift. This is actually what had been expected in contrast to the innovator's product where the physicians had in their hands and in their offices the Roche enrollment forms, the doctor enrollment forms. The primary opportunity for enrollment in the generic survey really comes when the patient fills the prescription and in that prescription, being a generic product, finds the generic enrollment form. So, as the generic enrollment forms come into greater use in the doctor setting, we see an increase in

doctor-generated enrollments.

[Slide]

The DAT1 questionnaire, as has been pointed out, reflects responses to the questionnaire at the onset of therapy. We will be looking at the DAT1, which is at the onset of therapy and DAT2, which is in the midst of therapy. The pregnancy risk categories which we established at the outset are reflected here: 5 percent of women had hysterectomy or were postmenopausal; 31 percent were not sexually active but using birth control; 23 percent were not sexually active and not using birth control; 39 percent of the sample were sexually active and using birth control; and only 1 percent was sexually active and not using birth control. If you look at the denominator restricted to sexually active women, the 1 percent becomes approximately 2 percent or 3 percent.

[Slide]

We created this photograph card in this multi-product environment to help respondents identify both the product that they were taking and

the educational materials that were presented to them. These become relevant in the subsequent slides.

[Slide]

The reported source of informational materials received at the outset of therapy really reflects the marketplace in the first year of the availability of generics, with 58 percent of the women reporting that the informational materials to which they were exposed were the Roche product; 18 percent Amnesteem; 4 percent Sotret; and 1 percent Claravis; in terms of none, 9 percent of women.

[Slide]

The medication guide was reported to have been received by 92 percent of women.

[Slide]

The information received in terms of pregnancy prevention, as has been indicated in the previous talks--99 percent reported that they were told to avoid pregnancy; 80 percent read the guide to contraception; 75 percent read the contraception knowledge self-assessment; 68 percent read the

emergency contraception information; only 7 percent reported watching the video about pregnancy prevention.

[Slide]

Forty-four percent knew about the isotretinoin information telephone line; 38 percent about the contraception counseling telephone line. Eighty-two percent reported that the doctor discussed contraception with them, and 19 percent reported that the doctor discussed emergency contraception.

[Slide]

Seventy-nine percent reported signing two consent forms. Recall that there are two consent forms for women, one a general consent and one specific to women. Six percent reported signing one consent form. Seven percent said they didn't sign any consent form and eight percent simply weren't sure.

[Slide]

We anticipated that many women would switch from Accutane to generic once the generic

drug became available. We also expected that many of these women would enroll in the isotretinoin survey during treatment prompted by the enrollment form in the generic package.

The DAT1 questionnaire was designed to assess compliance at the onset of treatment, not during treatment. For that reason, some questions in the questionnaire may be confusing to those enrolling during treatment and some of their responses may be inaccurate.

[Slide]

For that reason, we stratified the women according to their responses, at least for the next two slides, to this question: when in the past 12 months did isotretinoin treatment begin? Women who said my treatment began with my most recent prescription were called new users, and that is roughly half. The women who said that my treatment began prior to my most recent prescription were called prior users.

[Slide]

Because timing of pregnancy testing is

such a critical variable, we restricted it to the category of new users. Among those, 28 percent reported 1 test; 41 percent 2 tests. A significant proportion reported 3 or more and 9 percent of women reported none.

[Slide]

In terms of the timing, was the pre-treatment pregnancy test properly timed relative to prescription receipt, 82 percent would be considered appropriately timed; 10 percent had the test after the prescription was received; and 9 percent, as we said, had no test.

[Slide]

Primary contraceptive methods among the nonsurgical contraceptives is presented in this slide. Clearly, the overwhelming choice of contraception in all age categories is the oral contraceptive, representing roughly 70 percent in the 15-24 year-olds and 25-34 year-olds and still close to 60 percent among the 35-44 year-old women.

[Slide]

The number of contraceptive methods among

women who were sexually active since starting isotretinoin is presented here. The yellow line represents one method and there is a slight decline in the three most recent quarters, and that decline is actually reflected in an increase in the number of women reporting two methods.

[Slide]

Now I am going to talk about the qualification sticker. We are violating all rules of slide preparation quite deliberately because this is a verbatim text. It happens to be from the S.M.A.R.T. program but, as has been indicated, it is standard for all programs.

This is what the physician is indicating when he or she signs the qualification sticker. We have highlighted in yellow those portions that we think are the most relevant to where we are going, that a woman must have had two negative urine or serum pregnancy tests with a specified sensitivity before receiving the initial Accutane prescription, and that the second pregnancy test, a confirmation test, should be done during the first five days of

the menstrual period immediately preceding the beginning of Accutane therapy.

Where the first bullet reflects pregnancy testing, the second bullet reflects contraception in that the woman must have selected and have committed to use of two forms of effective contraception simultaneously, at least one of which must be a primary form unless absolute abstinence is the chosen method or the patient has undergone a hysterectomy.

[Slide]

Well, when we look at whether the sticker was present on the prescription, we see response rates that are comparable to what has been seen in other reports including the pharmacy audit, and 94 percent of women reported seeing a sticker on their prescription. Only 2 percent were clear that there was no sticker. Then, there was about 4 percent who couldn't be sure.

[Slide]

If we look at the presence of the sticker as a reflection of the patient-reported behaviors,

and I do stress this is patient-reported behaviors not necessarily the truth; there may be some misclassification, but among the women who reported a qualification sticker on their prescription, 68 percent reported that they were using two or more forms of contraception. Among the women without a sticker, 49 percent; 51 percent of women without stickers reported that they were using less than compliant forms of contraception; and 32 percent of the women with a sticker also reflected that they were non-compliant.

[Slide]

When we look at the pregnancy testing, and particularly the pregnancy testing and timing requirements rolled into one, which is what the qualification sticker...

[Pause for technical difficulties]

DR. CRAWFORD: While we are waiting for the audiovisual equipment, I would just like to state that you had mentioned a desire to provide a critique. If you can write up a critique and make sufficient copies for the joint committee and the

FDA staff representatives and give them to the FDA staff by early tomorrow morning it will be distributed to the committee for consideration.

DR. MITCHELL: If the committee were interested, I would welcome the opportunity to take ten minutes at some point to present it as well as to provide you copies.

DR. CRAWFORD: The chair tomorrow will decide on that. Thank you.

DR. MITCHELL: Okay, we would be happy to do that. Thank you. Someone made a comment and "DNK" is "do not know." I am sorry for not clarifying that.

I had just put this slide on when the goblins turned the computer off. Remember, we were talking about how the qualification sticker reflects patient-reported behaviors. We looked at contraception practices in the previous slide.

In this slide we are looking at compliance with pregnancy testing, and particularly with the timing requirements which are obviously not simple. This slide would suggest that only 26 percent of

the women reported compliance with the timing of pregnancy testing, no different from the women who didn't have a sticker. These data would suggest that the sticker itself is not a very accurate predictor of compliance.

[Slide]

Now focusing on the DAT2 or the interaction with patients in the midst of therapy, 96 percent, a high rate, continue to report the presence of a qualification sticker on their last prescription and 86 percent reported receiving a medication guide with their last prescription.

[Slide]

Interestingly, the behaviors prompted by information in the medication guide as reported by the women include changing their contraception method in 1/8; deciding not to have sexual intercourse with a male partner while taking isotretinoin, 16 percent; decided to have sexual intercourse with a male partner less frequently while taking isotretinoin, 6 percent; having a pregnancy test while taking the drug, 22 percent;

requesting more information on the drug, 5 percent; and requesting more information on contraception, 2 percent.

[Slide]

The pregnancy risk category comparison between the beginning of therapy and the midst of therapy is done for a couple of reasons, not the least of which is to try to obtain some reassurance that things aren't deteriorating once the initial education has been completed. Not surprisingly, the proportion of women who had a hysterectomy or were postmenopausal had not changed much, but there was some decline in the women who were not sexually active but using birth control. I would point out that that decline was, to some extent, made up by an increase in the proportion of women who were using birth control who had become sexually active.

Again, the concern is that a woman who declares that she is not sexually active at the outset of therapy may become sexually active and it would appear that that does happen, but those women had chosen to use birth control from the beginning

of therapy and, indeed, if you look at the small proportion we had shown before of sexually active women who were not using birth control, that has not changed from the beginning to the midst of therapy.

[Slide]

How many pregnancy tests in the past two months were reported by women still taking the drug at DAT2? One test by 12 percent; 50 percent reported 2 tests; and 13 percent reported no test.

[Slide]

Dermatologists accounted for 93 percent of the prescriptions; 2 percent by general practitioners; 3 percent by family practitioners; and less than 1 percent by other specialists.

[Slide]

In this slide we are presenting only the six total pregnancies that we identified through December 31. Recall that additional three pregnancies have been identified and forwarded to the manufacturers, who presented them today. Of the six, two women reported being pregnant at the

start of treatment; four women reported becoming pregnant during treatment, for a total of six.

We present the number of women completing the DAT1 and the number of women completing the DAT2 not to suggest that it would be a simple matter to calculate the pregnancy rate, and we would be happy to talk about the difficulties in deriving a meaningful pregnancy rate, but we present them here just to give you a sense of the numbers that we are dealing with. Clearly, more time needs to go by, we estimate 18 months from enrollment of the women in treatment until you will really know the pregnancy rate. This has been reflected by the FDA as well. If you estimate a 5-month course of pregnancy, a 6-month period in which to identify the pregnancies--11 months--for the woman to identify the pregnancy, and another 6 months to gather that information and query the women in detail about some of the factors related.

With that, I will stop and turn the podium over to Bob Pollock.

Isotretinoin Enhanced Risk Management Program

Program Elements for which Advisory Committee Input is Requested

MR. POLLOCK: Thanks, Allen. I appreciate the opportunity to address the committee on behalf of the generic manufacturers.

[Slide]

First I would like to thank the generic manufacturers and Roche for the method in which, in such a short period of time, they worked together to bring a proposal to you, and I want to stress that it is a proposal. I would like to further state that the generic companies fully support the 16 points of a consensus agreement that is described in the briefing document, and are committed to support whatever position is adopted by the joint advisory committee and ultimately by the FDA.

I would like to stress that this is a very unusual, and perhaps precedent setting, situation where it is being proposed that a widely distributed drug product is being brought under a mandatory registry system and represents the

introduction of a more complex program on top of a fairly recent change in the voluntary isotretinoin risk management program.

The agency's directive in our initial December, 2003 meeting was to evaluate the program to see how best to reduce the risk of fetal exposure. In that regard, the proposed risk management program proposed requires a mandatory 100 percent registry of physicians and all female patients, and provides a hard link to dispensing of isotretinoin at the pharmacy level to females of childbearing potential only when there is documented evidence of a current negative laboratory-based pregnancy test.

We request that the advisory committee provide advice on certain issues in an effort to help us strike a balance that will assure that the elements of the proposed program, when implemented, will not be too complex and burdensome as to cause practitioners to abandon the therapy that for certain patients is extremely valuable, and will also not create a potential access problem for

patients or make it impossible for them to navigate through, yet is stringent enough to significantly reduce the risk of fetal exposure.

[Slide]

In that regard, we would like the advisory committee to provide and discuss certain issues that we think are extremely important. One has to do with the registration of male patients in addition to female patients. Secondly, the component of the patient interaction with the educational and risk management evaluation component and, third, to discuss for us a firmer link between the registry and the pharmacist, perhaps through a pharmacy registration program.

[Slide]

In relationship to the registration of male patients, we would like the committee to take note of the fact that our focus was to reduce the risk of fetal exposure. Approximately 50 percent of the patients, as you have seen in data presented earlier, are male. We would also like to note that the sticker program, which would continue,

differentiates between male and female patients. I would also like to emphasize the fact that the educational components associated with male patients would continue as they are today.

[Slide]

Secondly, we would like your thoughts on the patient interaction with the educational and risk management evaluation component of the program. We would like you specifically to address what should be the purpose of this interaction. Should it be to reinforce education, or should it be to define and enforce compliance? By that, I mean if a female patient were asked a question, how many forms of birth control do you use and she answered one or none, should there be a "no drug" provision for an inappropriate response to an interaction? And, if there should be, how would we deal with the impact on the potential interruption of treatment program with the "no drug" provision confounded by a negative pregnancy test finding?

[Slide]

Lastly, in relationship to an issue

brought up by the agency in regard to a firmer link between the registry and the pharmacist, we would like you to address whether this is sufficiently addressed by the requirement of a hard link to a laboratory-based negative pregnancy test.

We would like you to also consider whether it would be appropriate to revise the isotretinoin label to state that it would permit dispensing only if the prescription is authorized by the registry for female patients and that the pharmacist must verify patient eligibility and obtain an authorization number for each prescription for a female patient through an interaction with the registry.

We would also like you to address whether or not the control factor in this regard should be the practice pharmacy or should there be a more restrictive requirement that may result in a restricted distribution system.

We appreciate very much your views on this and look forward to hearing your input. Thank you.

Questions to Roche and Generic Firms from Committee

DR. CRAWFORD: Thanks to each of the speakers. At this time we would like to open up the forum for questions from any members of the committee to any of the speakers who represent the sponsors. Dr. Strom?

DR. STROM: I have two questions. One is that we heard that in the S.M.A.R.T. system or its generic equivalents mail order wasn't allowed. Are there data about how much is being dispensed by mail order now despite the fact that it is not allowed?

My second question is for Dr. Mitchell but I don't know if you want me to proceed or wait for the answer.

DR. HUBER: I am Mary Huber from Roche. To answer your first question, mail order is not allowed.

DR. STROM: I understand it is not allowed. My question is how much is happening.

DR. HUBER: We are not aware of any dispensing via mail order.

DR. STROM: I mean, are you not aware or

do you have data? Given the increasing proportion of dispensing nationally that is happening by mail order, I am trying to get a sense of whether your system is being bypassed that way.

MS. REILLY: Tammy Reilly. The data that we get through sourcing of prescription information demonstrates to us that there is not mail order prescription coming through for the Accutane product.

DR. STROM: Okay. The second question is for Dr. Mitchell. Obviously, it is early in your new survey but if I did my seat-of-the-pants calculations correctly, it looks like there is on the order of 60,000 prescriptions per month generically being dispensed. If you assume the normal course is four months, that is about 15,000 new people a month getting it. Across 12 months that is about 180,000 patients who began a course of Accutane prescriptions, generic Accutane prescriptions, which would seem consistent with the data that FDA was presenting us in terms of total numbers in the market share data we were obtaining.

What we saw in the survey was 8,600 subjects. With the survey that is looking at 8,600 out of 180,00, I wonder if you might want to speculate, if you can, about how you think the people you are getting data from may be different in their compliance, and so on, from the much larger number of people you have been unable to get.

DR. MITCHELL: Clearly, that is a critical question and it is something that I would like to speak to more, if I am allowed to do that, but the brief answer is that the fraction of the target population that is enrolled, while informative, as anyone who understands epidemiology understands obviously, is not necessarily itself a reflection of whether it is representative.

The question of representativeness is a tough one to identify without having really firm information available and, as I said, I hope tomorrow to be able to touch on that. I would argue that in our older data where we had large numbers and an opportunity to do some comparisons, we actually found the data to be not

unrepresentative in the sense that women at higher risk were not preferentially being excluded from the survey. In fact, to give the punch line, we would argue that the survey might preferentially include women at higher risk, for reasons that I could touch on.

The issue of whether we can do much at this point with 8,600 women out of this universe is one that I simply can't answer because we are ramping up in our enrollments, as you have seen. The first enrollment came in essentially a year ago and we have been increasing enrollment substantially each quarter. I think what is necessary is to do the same kind of comparison on the data coming in to the generic survey that we had the opportunity to do for the Accutane survey with the previous 14 years.

Can it be representative? Yes, I would argue it could be. Is it? I think it is early to know and I actually shy away from rate estimation based on such a small numerator and denominator for all sorts of reasons.

DR. CRAWFORD: Dr. Cohen?

DR. COHEN: I would like to get back to something that you actually brought up right at the beginning of the meeting today, and that is what really is behind these failures? I am not hearing that yet. I think it is great to look at all the aggregate data from surveys, etc. That is important. But I know I have learned, and others have learned over the years, that if you can drill down and really learn through root cause analysis, asking at several levels why did this happen, you learn an awful lot.

I think I am hearing some of the recommendations or allusions to recommendations about, for example, an IND program under which this drug might be made available. I think, no matter what you do, if you don't have those reasons for what is going wrong you are going to have the same risk at least to some extent of pregnancy, etc. So, I really think it is about, you know, learning more about what is actually going wrong that causes these failures and not having two forms of birth

control, not having pregnancy tests done, etc., etc. It is not just about stickers. It is what is going on, and I think if we are going to make decisions like that, at least at some point before FDA reacts to this, this morning, we need to have more information.

DR. CRAWFORD: Thank you. We have five speakers in the queue right now. The next is Dr. Kibbe.

DR. KIBBE: I have some questions for Roche, if somebody feels like taking them. Some of them are pretty easy and some may be a little more complicated.

Currently do you have any estimate of how many countries worldwide allow the marketing of your product?

DR. HUBER: Most countries worldwide.

DR. KIBBE: Is there any country that has asked you to withdraw the product from the market? One of the suggestions here that we heard from one of our speakers was to take it off the market.

DR. HUBER: I don't specifically recall

any withdrawal in my memory.

DR. KIBBE: How many countries worldwide have a risk management system to help control this particular risk of teratological effects?

DR. HUBER: Most countries have some form of risk management. It ranges from labeling to other approaches. If I could actually have the slides on, please?

[Slide]

One of the issues is we see this wide variation, and what we do have in common and we try to put in place in most places is a patient education component, recommendations for pregnancy testing, and recommendations for contraceptive use. But how this then gets implemented into a program and the mechanisms of the distribution of the product, is widely divergent. For example, something like contraception, in some countries there is very well done contraceptive counseling by OB/GYNs for almost every patient who gets contraceptions; in other countries that doesn't exist. In some countries there is much better

certification of specializations than in others, plus, we are also dealing with a different health authority in each country.

So, what we have taken the approach of is we have identified the key themes here, the education, pregnancy testing, contraceptive usage, and then it gets adapted working with the local health authority.

DR. KIBBE: Do you have at your disposal a kind of a measure of which countries seem to be being effective relative to the problems that we are facing? I think I would be most interested in knowing what you see as the differences between how that country handles it and the way we handle it. Because, if we are going to make changes, it would be nice to see a system that works better and learn from it.

DR. HUBER: We have the numbers for pregnancies from the various countries. We will get those for you in a moment. But the thing I would like to do is urge caution in interpretation of these data.

[Slide]

First of all, I don't have the sales for each of these countries broken down so this is just raw numbers of pregnancies. What you see is that there are pregnancy case reports, exposed pregnancies, occurring in each of these. One point I would like to make is that on an individual country basis the actual use of the product is much lower.

The other thing is that the tendency for reporting of pregnancies in many of these countries is substantially different than in the United States. Then, the thing that makes it even more complicated is that the background pregnancy rate, for example in western Europe, is lower than the pregnancy rate of women in the United States. So, at the end of the day, while there are some numbers and we can look at them and these rates look better, what is interesting is that many of these programs are actually less restrictive than the current U.S. proposal but the number of reports is lower.

DR. KIBBE: Does that--

DR. CRAWFORD: Thank you. Dr. Kibbe, we need to move on.

DR. KIBBE: One more?

DR. CRAWFORD: Yes, the last one.

DR. KIBBE: Does that mean that if we wanted to have a more positive impact it might not be by directly impacting this drug but by impacting some other sets of behaviors?

DR. HUBER: We believe the fundamental thing we need to try to impact on now is the basic behavior around a patient becoming pregnant.

DR. CRAWFORD: Dr. Wilkerson?

DR. WILKERSON: A couple of questions, first of all to Dr. Huber also, what was your worldwide volume of sales prior to introduction of the generic substitutions? What was the dollar amount per year for this product?

DR. HUBER: I don't know off-hand. The majority was the U.S. from a dollar point of view.

DR. WILKERSON: And within a hundred million dollars how much was that?

DR. HUBER: I don't know.
DR. WILKERSON: Can you get that data?
DR. HUBER: I will see if I can get that number for you.
DR. WILKERSON: Okay. Now, the second part of my question is since the introduction of the product what studies have you done post-introduction to try to address this problem? What kind of clinical studies have been done to see what kind of best clinical practices are available to reduce this risk?
DR. HUBER: I am sorry, I don't follow your question. Clinical studies?
DR. WILKERSON: Since the introduction of the drug in 1982, post-introduction, what clinical studies have been done to determine best practices for reducing the incidence of pregnancy?
DR. HUBER: Clinical studies are not the way to address the behavioral issue. By definition, clinical trials are conducted in a very controlled environment. We know that in a clinical trial we can influence pregnancy avoidance,

contraception, etc. The problem is that when you go into the marketplace there are much less restriction; there is much less control. So, what we believe is the more appropriate approach is through things like the Accutane survey and now through our new proposal to collect data from the post-market environment and use that as a basis for changes to the program.

DR. WILKERSON: But we have tons of data. You still have to have best practices for community application of these programs. So, you don't have any studies in other words?

DR. HUBER: We do not--

DR. WILKERSON: In a community setting, what is the best practices--you don't have that?

DR. HUBER: Yes, sir.

DR. CRAWFORD: Dr. Whitmore?

DR. WHITMORE: Dr. Huber, I have a question for you. With regard to the implementation of the new plan, that sounds terrific. I think one thing that needs to be stated once again is that only 13 percent of people

were pregnant when they began Accutane so, in effect, the new program will only affect that 13 percent theoretically, unless you can come up with some data that your educational program will affect pregnancy rates during therapy.

DR. HUBER: We agree that pregnancy at the start is the smallest component. The 13 percent is probably a slight underestimate because one of the things we do see is pregnancies occurring in the first cycle. So, you will hear some people saying we think maybe a quarter of them are actually pregnant at the beginning because some of those that are occurring at the first cycle are actually within five, ten days. Those are patients who probably were pregnant at the time of initiation. We can debate that. But you are right, that is the smallest subset.

What do we think we are going to do for the latter part? The behavior part is definitely the hardest component. There are some precedents. I mean, for the S.T.E.P.S. program it is a different population but they do have this

interaction with the patients on education. What we see this as is that the patients have one educational opportunity now in the physician's office. We are seeing this as an opportunity to actually supplement that. Can I give you data that says this will improve contraceptive compliance? No, I cannot give you that data today. But we think that there is broader data in other settings where, if you increase the number of interactions and these other types of approaches, you can modify some behaviors.

DR. WHITMORE: May I ask one more question about that? With regard to behavior, we keep stating that the reason for pregnancy is behavior of the women who are on this drug. Are we certain of that? Is there evidence to support that such that those who are on Depo Provera do not get pregnant?

DR. HUBER: We have limited data on Depo Provera. The problem with Depo Provera is that it actually aggravates the acne so it is not widely used in this population. What we see as evidence

in the behavior, and I am answering your question indirectly and I apologize, is if you look at compliance with forms of contraception the current data shows that the women are not complying with the two forms of contraception. We clearly see that, and we have multiple sources. We see that in the Accutane survey data. We see that also with the pregnancy case failures. So, we think there is room for improvement in compliance in the need for two forms of effective contraception.

DR. CRAWFORD: Dr. Bergfeld, followed by Dr. Bigby.

DR. BERGFELD: Thank you. I have a question regarding the generic presentation. It implied that the inclusion of the survey in the package dispensed drug was better than the physician survey. Is that a correct statement for the population that was sampled? I mean, the population was relatively small. Is that a correct assumption?

DR. MITCHELL: I am sorry, I apologize if I gave that impression. Could you restate what

your concern was?

DR. BERGFELD: In one of your graphs you demonstrated that including the survey in the drug package dispensed by the pharmacist the compliance of filling out the survey was improved with that method over the physician.

DR. MITCHELL: No, no, that was not the intent at all. I was simply trying to reflect the source of the survey enrollment.

DR. BERGFELD: For that limited population, that limited sample--

DR. MITCHELL: Well, women in the generic survey, women who receive generic drug, whether they are prescribed brand Accutane or another brand, when they receive from the pharmacy generic drug, that is when they are most likely in the early months or implementation--that is changing over time but in the early months that is really their only source of an enrollment form for the generic survey.

DR. BERGFELD: At that time the drug Accutane could be substituted with a generic and

the information to the patient went through the pharmacist and the dispensing of the survey with the drug. Is that correct?

DR. MITCHELL: Well, it is my understanding that at that time and to this day a substitution is permitted, and often encouraged by the payers but the pharmacist merely dispenses the medication package for the appropriate brand. In that package is an enrollment form. In the Roche brand there is an enrollment form that goes to the SI/Degge folks. In the generic brands there is an enrollment form that goes to our survey. The same is true in the materials provided to physicians. Physicians have materials provided to them by Roche which include enrollment in the Roche Accutane survey. If they use the generic educational materials there are enrollment forms in those materials that will go to our survey. If it is confusing, I apologize but it is confusing.

DR. BERGFELD: Thank you.

DR. CRAWFORD: Dr. Bigby? I would like to remind the speakers to please turn off your

microphone after you have spoken.

DR. BIGBY: I actually have three questions. But I have a question for the chair for the moment. Is this the only opportunity that we are going to have to ask questions?

DR. CRAWFORD: Oh, no. We have a full day with all the representatives from the sponsors here tomorrow as well.

DR. BIGBY: Okay. So, for my first and most important question I would like a response from Dr. Huber and also from Mr. Sisto. That is, what is your goal of the new proposed program? Put another way, if we convened a year from now or a year after the program is implemented, at what number or rate of pregnancies would you consider the program unacceptable and a failure?

DR. HUBER: The overall goal remains a decrease in exposed pregnancies. With regards to a specific number, we are not prepared to do that today. That is something that is going to need to be discussed with the FDA and with other bodies. Your input would be helpful on that. What we are

concerned about is we have all recognized that there is an under-reporting element here. If we put in a 100 percent assessment program the actual numbers of pregnancies that are reported--not the number that are necessarily current but the numbers reported is likely to increase in the first year or so of the program. What we wouldn't want to do is design an effective program that we basically make a decision on, doing something negative about, on the basis of actually a much improved assessment activity. So, we realize that is the long-term goal but to provide a specific number that we would target for a year from now, we are not comfortable with that at this point.

MR. SISTO: And I would agree with what Dr. Huber said. We were given the charge of trying to come up with something that perhaps could enhance the existing program to try to reduce the number of pregnancies but, again, with having 100 percent control over the number of patients it is important to just understand that the reporting of those pregnancies may go up. We don't know how

long that may occur. Therefore, to be able to determine what an acceptable rate may be at this time, I just don't think is possible.

DR. CRAWFORD: Before we continue, I need to make an announcement, please. The Federal Register notice for this meeting announced that the open public hearing session would take place today between 11:00 a.m. and 12:00 noon. However, three registered open public hearing speakers gave their presentations at an earlier time this morning. The Executive Secretary has informed me that no additional speakers have signed up to speak during today's open public hearing session. In the interest of fairness, I would like to provide the opportunity at this time for any other member of the public to speak. Seeing none, we will continue with the questions from the committee. I do want to say that it appears that almost all the other members of the committee are in the queue and we will take as many questions and comments as we can before our lunch break.

DR. BIGBY: I wasn't done. I had three

questions.

DR. CRAWFORD: I am sorry, Dr. Bigby will continue, followed by Dr. Gardner.

DR. BIGBY: To the same two responders, what component of your new program will actually result in a decrease in the number and rate of pregnancies?

DR. HUBER: There are two things that are aimed specifically at reducing the pregnancy rate. The first is the smaller component, granted, the 13 percent of women who are pregnant when they receive that prescription. We feel very confident that requirement of a laboratory-certified test, pregnancy test, within a specified window will close that for almost all patients. So, we feel very strongly that we can have an impact on the majority of those.

[Slide]

What we need to look at though is that other component. What we are building on--if you notice here, that was that first patient visit. This is analogous to the current S.M.A.R.T. The

issue with the current S.M.A.R.T. program is what it does is it gives a one-time opportunity to the physician to educate the patient but there is no testing or follow-up for whether the patient retained that information; have they understood that information; are they complying with that information. We see this interaction with the registry here as an opportunity to actually assess that knowledge.

We think this will have an impact in two ways. One, as we have heard several times, the need for more data. What is the root cause, is I believe how you stated it. What we are looking for is are there certain specific behavioral components? Are there answers to questions? Are there specific things that we can identify when we gather this data on all patients on an ongoing basis that tells us who are the patients at risk so we can do a specific intervention?

But the broader benefit is that this serves as a reminder to the patient. You have now added an additional repetition of the message to

the patient every cycle through the treatment. That is what we see as the primary impact of the program.

DR. CRAWFORD: We need to move on. Right now I am going to ask that the committee members please try to ask just one question, perhaps with a quick follow through. I believe one of the sponsors wishes to reply. Dr. Gardner, please get ready.

MR. SISTO: The generic companies agree that the two biggest things would be the constant interaction for the reaffirmation of the educational component of the program, and also the hard link to the pregnancy test. Those two items would be very critical to that enhanced issue.

DR. GARDNER: Dr. Huber showed us a slide that had two points about isotretinoin indicated for severe recalcitrant nodular acne for people who are unresponsive to conventional therapy. I am still trying to understand who is at risk here. So, my question is do you have an estimate of how many people with that characteristic there are and

how many of those are women of childbearing age.

Secondly, we have heard a lot about behavior and I would like to ask about corporate behavior. Does your company, or any of them, currently have a direct to consumer advertising program for these products? Thirdly, I think you were going to respond to Dr. Wilkerson's third question.

DR. HUBER: I may have Ms. Reilly respond to your second question about direct to consumer advertising. If I remember your first question, it was regarding the incidence or prevalence of severe recalcitrant nodular acne. As was pointed out by the previous speaker, unfortunately, that data is not readily available for incidence or prevalence. The issue, as she pointed out, is that the ICD-9 code does not distinguish between moderate and severe recalcitrant nodular acne. So, when you try to go back in the databases, most of them are based on this coding so what you get is a mixture of both of those diagnoses.

With regard to your second question

regarding direct to consumer advertising, Ms. Reilly?

MS. REILLY: The answer is simply no, we do not have direct to consumer advertising for this product.

DR. CRAWFORD: Dr. Katz?

DR. KATZ: I have a question to Dr. Huber and a comment on Dr. Bigby's comment. Could you just clarify what would be involved with the patient ID proposal and the interaction with the registry that you are proposing?

DR. HUBER: The patient number would be a unique number generated by the system. We do not want to use things such as social security numbers, etc. because that gets us into other issues. So, our intent is that the physician would interact with the system.

DR. KATZ: How would that be? Telephone call?

DR. HUBER: Well, the details of that are something we need to work on. It would probably be an interactive voice system but there are also

web-based technologies that are doing this. It may be a mixture of the two that allows whichever would be the more convenient--

DR. KATZ: In other words, it would be picking up the telephone and saying this patient is qualified, has had a pregnancy test--

DR. HUBER: Right, and there would probably be a few questions they would answer and, because they are a registered physician, they would enter their physician code so that the system knows that it is a registered physician and in response back they would get a number for that patient.

DR. KATZ: And what about the interaction with the registry? You said that the physician--you used the term health provider, but the doctor initially has the interaction with the patient and that is the last time. I heard implied that that is the last time that there is real interaction and then the patient would interact with the registry. What would that involve, patient interaction with the registry?

DR. HUBER: Could I have the slide on,

please?

[Slide]

I know this is tough to follow from a distance. This is patient visit one. This is the initial visit. This is what I am referring to where the physician enters his information and gets the patient ID number back.

This second interaction is outside of the physician's office, or it can be outside of the physician's office. This is a patient interaction via web or telephone with the registry. The registry is this amorphous box across the top here.

DR. KATZ: Who would initiate that? The patient?

DR. HUBER: Our intent at this point in time is that the patient would take their identification number, call in, identify themselves using their number and initiate it. There are actually technologies we are investigating which would allow the system, on a periodic basis, to trigger the call back. That would be something we would work on.

DR. KATZ: Why would the patient prefer to call the registry rather than call the doctor with a question? I mean, ordinarily as a practicing physician, it is not too outlandish when we finish a visit to say, by the way, I will see you in four weeks. If you have any questions before then, give me a call, and generally they do. Why is there this interaction with the registry?

DR. HUBER: The intent of this is not to replace the patient asking questions of the physician. What the purpose of this middle visit here, and there is another physician visit here, is, shall we say for lack of a better word, almost like a testing. It is ensuring through a series of interactions that the patient has understood what they have been instructed on. Clearly, we still think the primary relationship is between the physician and the patient and if the patient has a question they should always go back to their physician. The interaction with the system is merely to indicate before dispensing that the patient has some understanding of what they have

been told.

DR. KATZ: As a physician of 34 years, that is very foreign to me.

DR. CRAWFORD: Dr. Katz, can you hold it until tomorrow because we have a lot of time tomorrow? Thank you. Dr. Sellers?

DR. SELLERS: We have acknowledged that the data from the survey is very limited, and in the materials we received prior to the meeting the FDA illustrates why this data is not generalizable. So, at best, the information that we have seen is merely hypothesis generating. That concerns me because the proposed risk management programs that we are hearing about today rely heavily on the qualification stickers. During the presentations by Roche and also by the generic manufacturers we heard reports of 96 percent and 97 percent where the qualification stickers were filled out properly or correctly completed. But exactly what that means was not defined. In fact, Dr. Ackermann Schiff referred to the last negative pregnancy test, not whether it was a baseline or follow-up

test.

So, my concern is, number one, how this assessment of the efficacy of the qualification stickers was made and the fact that we are using that as a basis for the new programs may be problematic. In fact, in the S.M.A.R.T. package, and as it related to the question I asked earlier, under the qualification date--this is in the S.M.A.R.T. briefing package, Table 1, on page 62, the use of pregnancy tests and Accutane qualification stickers, under the qualification date it is listed as that date that a sample was taken for the confirmatory negative pregnancy test, not the date when a negative pregnancy test was actually obtained. So, I do have concerns over the qualification process and I hope that we address this further. Thank you.

DR. CRAWFORD: Did you want a response right now? No? Dr. Honein?

DR. HONEIN: Thank you. I had a question for Roche about the transition that went on in the fall of 2002. If I understood correctly, around

six months into the S.M.A.R.T. program you transitioned from Slone to the Degge Group. I was wondering if you could comment on how that may have impacted evaluation of the first-year S.M.A.R.T. and, in particular, how long you think or you know dual materials might have been on the marketplace, such as in prescribers' offices or in the medication packets, for those two Accutane surveys?

DR. HUBER: There was a transition during the period described. With regards to the impact on pregnancies, we don't have any data that says there was an impact.

DR. HONEIN: Sorry, I wasn't asking about an impact on the pregnancies but an impact on evaluating the first year of the S.M.A.R.T. program and how the various metrics were working.

DR. HUBER: With specific regards to the metrics? The primary metric failed. That was the one that 60 percent of the patients would enroll in the survey. We did not achieve 60 percent. There was an increase in survey participation with the transition of the program but we still did not

achieve the 60 percent. The metrics of the Accutane survey I believe is what your question was, correct?

DR. HONEIN: Well, I want to know in general how you think it affected your evaluation of the first year of S.M.A.R.T. to have this transition about six months into that year. One example that I was wondering about is for how long in some prescribers' offices did they still have the older Accutane survey S.M.A.R.T. materials and not the new ones, and how all of that was handled.

DR. ACKERMANN SHIFF: When we switched we were in a single source environment so the switch between the packaging of the Accutane survey through SEC to SI/Degge occurred in a single source environment. In addition, the switch happened at the pharmacy level where the pharmacist provided new enrollment cards with the correct enrollment information.

DR. HONEIN: And the prescriber enrollment forms, was there any issue there?

MS. REILLY: When we switched to the new

program all of the enrollment materials were exchanged at the physician office by the sales representatives that were working for Roche at the time. So, they would go in, basically offer them new materials and retrieve the old materials. That was the process.

DR. CRAWFORD: Thank you. We are going to move on now. The Executive Secretary has told me that we can go until 12:10 and we have about five more speakers who have requested to speak. The next ones will be Dr. Epps and then Dr. Schmidt.

DR. EPPS: Thank you. I will try to be brief. As a pediatrician and dermatologist, I will tell you that adolescents are a unique population and surveys can be helpful but I think the survey that was enclosed here--if you all haven't read it very carefully--is extremely personal and explicit: have you interacted with someone in the last three months? Was the male fertile? Has he had a vasectomy? Those are questions that not a lot of young people are going to want to answer and not a lot of adults are going to want to answer either.

So, they sometimes may tell you what they want you to hear.

Also, a frame of reference would be the concept of time. Sexually active may be ever; it may be within the last two weeks. That is also true of contraceptive use. I used two the last time; I may not use any the next time. So, at the time of the survey you may be getting the best information that you can get and that will certainly affect the results of your survey not only for the concept of time but also for honesty because sometimes they will put down what they think you want to hear and they will put down what they think their parents want them to put down.

I am also very concerned about confidentiality with the registry identification numbers. Most people will tell you, certainly in the D.C. area, that they don't think that confidential means confidential.

DR. SCHMIDT: There is something about drinking the water of the Potomac that makes me want to ask just definitions of simple words, and

the one word is pregnancy. In one of our handouts a person was considered pregnant by a urine pregnancy test at home. It has been my feeling that urine pregnancy tests can have 10 percent false positives if there is protein or blood in the urine. I would like to ask in these defined pregnancies how are they defined as pregnancies.

The second thing is that I would like to back up how unusual teenagers can be. I know; I have had some. I gave my son Accutane and I almost had a heart attack when I went to the drugstore to pay for it. One of the challenges of all this is how are we going to pay for it. I just throw this out to the group.

Then, my third thing is the glossary on Pub Med that I reviewed before I came here. It has almost 140 papers on this and it sounded like we are trying to go into a registry like thalidomide. And, there was a reprint that I couldn't find because we don't have it in the Texas Medical Center Library that says "thalidomide and isotretinoin--why treat them differently?" and it

is in Reproductive Toxicology. And, I would like to ask if Hoffmann-La Roche or somebody could get a copy of that for us to review while we are here.

DR. HUBER: We will certainly try.

DR. SCHMIDT: Thank you.

DR. CRAWFORD: Dr. Shapiro?

DR. SHAPIRO: I am not sure who I am directing these questions to, but I will be brief. From an ethical and a legal perspective, clearly the most difficult aspect of everything we have talked about is requiring and/or tracking contraceptive behavior. That leads me to emphasis on the informed consent process, which is more than a form as everybody knows. I am wondering whether any analysis about the video and the other available media for enhancing that process has been done in terms of impact on contraceptive behavior in the group we are studying, and whether further thought has been given to checking understanding prior to receipt of the prescription but after the informed consent process to see where we can make that better and more effective. That is one group

of questions.

The second has to do with the teeth in all of this, so currently and also with respect to the proposed plan what happens theoretically and what happens really and what needs to happen when a prescription is filled without a sticker, or a physician qualifies a patient when that patient should not be qualified, and so forth.

DR. HUBER: With regards to your second question first, with the qualification sticker there is no punitive means available if a pharmacist fails to report. We are limited basically to practice of pharmacy at state level. So, if pharmacists are not complying with the labeling we can simply report them.

One of the advantages of our proposal that we put forward today is that that would then get linked back very specifically prior to dispensing to the registered pharmacist. In the current approach the pharmacist does not do a letter of understanding. In the new proposal they would have to do a letter of understanding of what their role

was in order to get a registration number.

DR. SHAPIRO: Can I just ask a further question? With respect to both the doctor and the pharmacy, there are examining boards in every state, as you said. So, do you report or would you report or do you think you should report?

DR. HUBER: I am not aware of us specifically reporting anybody, but I am also not aware--we have seen isolated examples of errors on stickers. I am not aware of any systematic failure that we have seen where we have clearly become aware of somebody intentionally, willfully, continually going around the program. So, at this point in time, we think the mistakes are happening in the current system. That is why we propose to change the overall system. If we thought it was limited to one or two shall we say bad apples, I think we would probably propose a different approach than we did today.

DR. CRAWFORD: Thank you. Mr. Levin and our final question before lunch may be Dr. Ringel's.

MR. LEVIN: I will be brief. I guess I am confused on the logistics of the Roche proposal. I thought at first you were suggesting that the registry would actually receive some sort of hard copy, so to speak, of the pregnancy test result. Then you talk about calling in and the communication with the registry is by phone and the two don't match up.

DR. HUBER: The primary interaction for most of the interactions is, indeed, phone or web-based. The laboratory test result, because of time compatibilities--we discussed things like faxing the lab slip but you start creating some logistical issues. So, this is a detail we would be happy to hear your advice on, but our thoughts are at this time that basically it would be the physician entering the lab test but then there may be some follow-up. In other words, you would have to send the form in to reinforce that it was there. That is one of the details we will be discussing in the design of the system.

MR. LEVIN: I think it is more than a

detail because you are hanging an awful lot of this program on that issue--

DR. HUBER: Yes.

MR. LEVIN: --and it is much more than a detail; it is central to that part which you are suggesting is the big improvement of the program.

DR. HUBER: In the registry we want evidence that a laboratory pregnancy test was obtained. How that gets in there, via a fax or via some other mechanism, is something that we need--we are not sure what the best mechanism is to do that today.

DR. KWEDER: I can follow-up on that. There will be some discussion later today and tomorrow, I believe, of some of the tools that can be used. There are other programs that employ them.

DR. CRAWFORD: Dr. Ringel?

DR. RINGEL: I suppose this is a related issue, but one of the problems with the program now is patient non-compliance and one is physician non-compliance. Clearly, physician non-compliance

is at least in part due to physician frustration with the difficulty of using the system. It is important, whatever system we put in place, to do a walk through and try to imagine what is really going to happen. I did that a little in my head with the system that is here.

I will go through this briefly. In the initial visit the physician is required to register the patient during that first office visit, which means that he or she has to take time off from what they are doing to get on the phone to do this registration. I don't know how long it is going to take. It may take a while to get through. That is going to be difficult.

For the patient to have the second visit, that can't be scheduled because it has to be done during a patient's menstrual period so that is going to be an urgent call to the physician who is then going to have to fit the patient in.

The laboratory pregnancy test won't be back that same day so the physician can't possibly write the prescription on the same day that they do

the test. So, that is yet another trip or phone call, or whatever.

When you give a patient an Accutane prescription for 30 days you can't see them back in 30 days because they have to get it filled, plus the fact that maybe 30 days is a Sunday. So, to be on the safe side you have to make the appointment for 26, 27 days and after a while you get into what I think of as appointment drift. You keep on making it earlier and earlier and patients keep on collecting more and more pills until at the end they are left with extra pills that they haven't taken, which is something we really don't want.

That is not to even mention all the other real-world problems such as it snowed on my appointment day, I can't get there. The physician is on vacation that week. What do we do then? College students I have found to be an enormous problem; rural settings where people travel over an hour to get to their physicians. Whatever system we have, we need to walk through it and make sure that this is really something that is practical,

otherwise physicians are not going to cooperate and, like most biologic systems, as much as the test may be very good, the biologic systems find a way to wriggle around it.

DR. CRAWFORD: Thank you. You may notice that Dr. Gross has returned and, as I said, I wasn't giving it back easily. I want to make an apology to five of our committee members who had questions or follow-ups and I am going to ask that Dr. Gross place you on the list for tomorrow.

At this time, if FDA has no additional input, we will break for lunch and I have been told that the meeting will reconvene promptly again at 1:00 p.m. Thank you.

[Whereupon, at 12:15 p.m., the proceedings were recessed for lunch, to reconvene at 1:00 p.m.]

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

DR. GROSS: The first speaker is Dr. Marilyn Pitts, who is a safety evaluator for the FDA. She will talk about isotretinoin pregnancy exposure: spontaneous reports one year pre- and one year post-the risk management program.

Isotretinoin Pregnancy Exposure: Spontaneous Reports One Year Pre- and One Year Post Risk Management Program

DR. PITTS: Thank you. Good afternoon.

[Slide]

Over the next hour the Office of Drug Safety will provide two presentations. I will lead with a presentation entitled isotretinoin pregnancy exposures: spontaneous reports one year prior to and one year after implementation of the current risk management program. I will be followed by Dr. Allen Brinker who will present the isotretinoin pregnancy prevention program evaluation, to include an analysis of the prescription compliance survey, as well as an analysis of the isotretinoin surveys.

[Slide]

My presentation is from collaborative reviews by myself, Dr. Claudia Karwaski and Dr. Aaron Mendelsohn of the Office of Drug Safety.

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I will provide the objectives of the presentation, the methods that we used to analyze the data, a description of the limitations to the data, as well as the results of the spontaneous adverse event reports of the women who were pregnant while using isotretinoin. I will focus on pregnancy testing, contraceptive use and pregnancy and fetal outcomes. I will also provide drug use data and offer conclusions.

[Slide]

My objectives are to compare the spontaneous adverse event reports of women who were pregnant while using isotretinoin. I will compare reports received one year before the implementation of the current risk management program to one year after implementation. Additionally, I will provide information concerning isotretinoin drug use during the same time periods.

[Slide]

We identify cases for analysis by searing the AERS database, as well as requesting the manufacturers of isotretinoin to submit pregnancy exposure reports. We identified all reported cases of maternal exposure where exposure occurred during isotretinoin treatment or within 30 days of discontinuation of isotretinoin. All identified cases were reported by August 15, 2003.

We categorized cases by conception date into three groups. Differences in categorization resulted in the manufacturer having different cases in their case series. The prior risk management program cases included reports of conception dates from April 1, 2001 to March 31, 2002 and the current risk management program included cases with conception dates from April 1, 2002 to March 31, 2003. We placed in the unknown category those cases where the conception date was unknown or could not be determined.

[Slide]

We included in our analysis 325

self-reported cases of women who were pregnant while using isotretinoin. We believe these 325 cases represent a fraction of what occurs and the true number of isotretinoin exposed pregnancies is unknown. Of the cases that provided sufficient conception date confirmation or the conception date could be estimated, we analyzed 127 cases during the prior risk management program and 120 cases with the current program. Seventy-eight cases lacked sufficient conception date information to categorize and were, therefore, placed in the unknown category.

[Slide]

This slide is a little busy. The important point on this slide is the "total" column where we see that the majority of pregnancy exposures were reported directly to the manufacturers, followed by a smaller number reported to the isotretinoin surveys. We note an increase in reporting to the isotretinoin surveys when the current program is compared to the prior program.

[Slide]

Again, to conduct our analysis we reviewed spontaneous adverse event reports. Before proceeding to discuss our findings, I would like to describe some of the limitations of using case reports. Case reports are subject to variable reporting. Reporting can be influenced by a number of factors, including but not limited to publicity surrounding the drug product, as well as the length of time a drug product has been on the market. Case reports are also subject to variable quality and information as well as variable completeness of the information provided. Additionally, for this review in particular the case reports lacked risk management program specific information to guide the reporter in providing data. As such, the experience of the women who were pregnant in our case series may not represent the general isotretinoin user.

[Slide]

This slide provides information concerning the age of the women who were pregnant while using

isotretinoin. There is very little difference in the ages of the women who experienced isotretinoin exposure under the current risk management program when you compare to the prior program.

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In the women who were pregnant while using isotretinoin we analyzed the timing of conception in relationship to the time of isotretinoin treatment. In other words, when did the women become pregnant while using isotretinoin? In the cases that provided sufficient information, we found that women became pregnant throughout isotretinoin treatment. A small number of women were already pregnant when they started isotretinoin. For the 20 women who were already pregnant when they started, we found fewer cases in the current program when you compare to the prior program. For the women who became pregnant during treatment we found no appreciable difference between the programs. Moreover, when we looked at the individual months when women became pregnant, the largest number of women became pregnant in the

first month of treatment under both programs. We did not find any appreciable difference in the number of women who became pregnant within 30 days of discontinuation.

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In the women who were pregnant we analyzed the duration of exposure of the pregnancy to isotretinoin. Of note, less than 50 percent of all reports provided sufficient information to make this determination. Of those reports that provided sufficient information, we see a wide range of the duration of exposure, from up to three months in the prior program to up to two months in the current program. Although the range of exposure is wide, the median time of exposure was the same for both programs.

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I would like to shift our focus now to pregnancy testing in the women who were pregnant while using isotretinoin. Currently, the isotretinoin label requires two baseline pregnancy tests prior to initiation of therapy. The first

baseline pregnancy test is a screening test that should occur at the time the decision is made to pursue treatment. The second baseline test is a confirmatory test that should be obtained during the first five days of the menses immediately preceding initiation of treatment.

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We reviewed the cases with pregnancy test information. We found that almost 50 percent of reports in both series did not provide sufficient information. Of the reports that did provide baseline pregnancy test information, we found that 50 percent of women in both series reported having any baseline pregnancy tests. However, when we looked at adherence to the label recommendations of two baseline pregnancy tests, we found that the majority of baseline pregnancy testing did not adhere to the label. The majority of women who had baseline pregnancy testing only had one test in both the current program and the prior program. Only a small number of women had two baseline pregnancy tests as recommended by the label, and

more women in the current program had two tests compared to the prior program. We didn't find a significant difference between the two programs in the number of women who reported not having a baseline pregnancy test.

[Slide]

Baseline pregnancy tests should prevent women from receiving isotretinoin if they are already pregnant at the start of treatment. In an earlier slide we saw that there were 20 women who were already pregnant prior to starting therapy. Twelve cases were in the prior program and 7 cases were in the current program. We looked closely at those cases and found that 16/20 women reported having at least one baseline pregnancy test and 9 of those women reported having two tests. Of 11 women who reported the results of the baseline pregnancy testing, we found that 8 had negative test results and 3 had positive test results. We also found that 14/16 women reported not having a baseline pregnancy test during the first 5 days of menses before starting isotretinoin as recommended

by the label.

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In addition to baseline pregnancy testing before starting treatment, once the patient has started treatment the current label requires monthly negative testing for the female patients to continue receiving isotretinoin prescriptions. Pregnancy testing while taking isotretinoin does not prevent pregnancies but serves to limit exposure of the pregnancy by facilitating detection and limiting supply of the teratogen.

[Slide]

In the cases of the women who were pregnant while using isotretinoin, we reviewed the case reports for any pregnancy testing during treatment. Pregnancy testing during treatment is a strategy for early detection and does not necessarily prevent pregnancy. Please note that 60 percent of the cases in both series did not provide sufficient information. Of the cases that did provide pregnancy testing information during use, we found that slightly more women in the current

risk management program reported any pregnancy testing during treatment when compared to the prior program. We also found that there was no difference in either program in the number of women who reported no pregnancy testing during treatment.

[Slide]

Now we turn our attention to contraceptive use in the women who were pregnant while using isotretinoin. The current isotretinoin label requires at least two forms of safe and effective contraception, one of which should be a primary method. Primary methods include hormonal contraceptives including tablets, injections, implants, patches and vaginal rings, as well as the IUD and male and female surgical sterilization. Additionally, contraception should start one month prior to treatment, continue throughout treatment and continue for one month after discontinuation of treatment. There are two exceptions to the contraception requirement, if a woman is practicing absolute abstinence and if a woman has had a hysterectomy.

[Slide]

In the women who were pregnant while using isotretinoin, we found that one-third of all reports did not provide information concerning contraceptive methods. Of the women who reported using contraception, we found that slightly more women in the current program reported using any method of birth control compared to women in the prior program. Additionally, there were fewer women in the current program who reported abstinence or not using any birth control method.

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However, when we look at those women who were using any type of contraceptive method, we found that the majority of women in both programs, contrary to label recommendations, used only one method of contraception, with that method usually being the primary form. We also found that a small number of women in both programs, as recommended by the label, used two methods of contraception.

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A small subset of women provided

additional information concerning their use of contraception. We found that slightly more women in the current risk management program reported non-adherence to contraceptive directions when compared to women in the prior program. We also found that a small number of women in both programs equally reported contraceptive failure. We define contraceptive failure as a pregnancy occurring even when the woman adhered to directions for use of the contraception.

[Slide]

We now turn our attention to pregnancy and fetal outcomes.

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Although we present this information in a comparative tabular format, once pregnancy exposure has occurred we recognize that no aspect of the prior or current risk management program necessarily had a direct impact on these outcomes. Please note that in 50 percent of all women who were pregnant while using isotretinoin the outcome of the pregnancy is unknown. We include in this

unknown category cases that are lost to follow-up, cases where the pregnancy is ongoing at the time of the report, and cases where the outcome was not reported. In the cases where we do know the outcome, we found that the majority of pregnancies ended in termination, either elective or spontaneous. We find that 29 pregnancies, across this row, ended in live births.

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Again, aspects of the risk management program are not expected to impact fetal outcome once exposure to isotretinoin has occurred. We found that at the time of reports the majority of babies born were reported as normal. It is unknown if any of the normal babies later exhibited developmental delays. We also found that 7 babies were reported abnormal, with 4/7 having abnormalities in organs affected by retinoids. The remaining 3/7 abnormalities reported were not consistent with retinoid effects. Again, the fetal outcomes were at the time of the report and may not reflect any additional developmental delays that

have been reported with retinoid exposure.

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We also looked at isotretinoin drug use for a one-year time period before implementation of the current risk management program and a one-year period after implementation. We obtained prescription utilization data from IMS Health, Inc. and AdvancePCS.

We used IMS National Prescription Audit Plus. National Prescription Audit Plus data measures the outflow of dispensing prescriptions from pharmacies to consumers in retail stores, mail order stores and long-term care facilities. Just to make a note, this is the source of the data. It doesn't necessarily mean that isotretinoin prescriptions came from any of those particular areas but this is where the data comes from.

Data are obtained from a sample of approximately 22,000 pharmacies in the U.S., which represents approximately 45 percent of U.S. prescriptions. Data from NPA Plus are projected nationally.

[Slide]

We also obtained data from AdvancePCS. Advance PCS is a large U.S. pharmacy benefits manager that covers more than 50 million patient lives and over 300 million prescriptions annually. Data are obtained from paid prescription claims for those patients with prescription drug benefits administered by AdvancePCS.

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There are limitations to using this data. The data do not permit a more detailed analysis of the observed trends. Additionally, national estimates from IMS Health may be variable due to small numbers in certain subgroups, and AdvancePCS data may not be nationally representative.

[Slide]

We found that for the year following implementation of the current risk management program the number of prescriptions decreased by 23 percent compared to the previous year. We also found that the number of refills decreased from 16 percent to 2 percent. This is important because

the current risk management program does not allow for automatic refills. Additionally, we see the arrival of generics to the marketplace during the current program. However, the generic product labeling is consistent with the innovator's label with respect to elements of risk management. The level of prescribing by dermatologists remained unchanged and the percentage of women who received prescriptions remained unchanged.

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In conclusion, we found that the number of prescriptions dispensed for isotretinoin decreased by 23 percent following implementation of the current risk management program. We also found that the number of refills decreased from 16 percent to 2 percent, demonstrating increasing adherence with the label recommendations of no automatic refills. We found that other utilization variables such as gender or prescriber did not appear to be influenced by the implementation of the program.

[Slide]

For pregnancy exposures we found that the actual number of women who were pregnant while using isotretinoin did not decrease appreciably, especially since there has been a modest decline in the number of isotretinoin prescriptions dispensed for the same time period. We found in the current risk management program a slight decrease in the number of women who reported being pregnant prior to starting treatment. We also found that pregnancies continued to occur throughout isotretinoin therapy for both risk management programs.

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In the women who were pregnant while using isotretinoin we found no reported difference in the duration of exposure of the pregnancy to isotretinoin when you compare programs. Additionally, we found no improvement in baseline pregnancy testing, however, we did see a slight improvement reported in pregnancy testing during isotretinoin treatment as well as a slight improvement in the reported use of one method of

contraception.

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However, we found that only 15 percent of the 325 women adhered to the label recommendations of using two safe and effective methods of contraception. Finally, we found that of the women who reported contraception information, 38 percent reported non-adherence to the healthcare provider's instructions for use.

Again, we used spontaneous adverse event reports to conduct our analysis. Although valuable, there are limitations to the use of case reports as previously discussed. The experiences of the women in this case series who were pregnant while using isotretinoin may not be representative of the general isotretinoin user.

DR. GROSS: Thank you very much. The next speaker is Dr. Allen Brinker, lead medical officer for epidemiology in the FDA. He will talk about isotretinoin Pregnancy Prevention Program evaluation.

Isotretinoin Pregnancy Prevention

Program Evaluation

DR. BRINKER: Good afternoon. Like Dr. Pitts, I am with the Office of Drug Safety.

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I will be discussing this afternoon the isotretinoin Pregnancy Prevention Program evaluation, both the prescription compliance survey and the patient survey.

[Slide]

First I would like to recognize our collaborators, Cynthia Kornegay and Parivash Nourjah. I would also like to recognize the contributions of Dr. Karen Lecter and Dr. Mark Avignon.

[Slide]

I will begin by describing the prescription compliance survey or PCS, and then move to the patient survey. In keeping with previous speakers, I will utilize the expression current RMP, current risk management plan, to refer to the risk management plan for isotretinoin as implemented on April 1, 2002.

[Slide]

Beginning now with the PCS, first I will present a brief summary of the survey design and major findings. I will then discuss the major methodological issues of the survey and also talk about issues with the audit portion of the PCS. Finally, I will discuss the major conclusions of the analysis.

[Slide]

The PCS was conducted by the Accutane sponsor for the Accutane brand isotretinoin prescriptions. The primary outcome of interest is compliance with sticker use, which is defined as the presence of an Accutane qualification sticker on the prescription. Secondary outcomes are the completeness of the sticker and whether or not the information on the sticker is correct.

It should be noted that the PCS was only intended to measure compliance with qualification stickers, which are just one component of the current RMP. Compliance with qualification sticker use was never intended to be used as a complete

surrogate for compliance with the totality of changes implemented with the current RMP.

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Design of the PCS--the PCS is a retrospective, repeated-measure study which will recruit in total some 6,000 randomly selected U.S. pharmacies, stratified on selected criteria so as to be representative of all U.S. pharmacies. Data collection takes place four times a year for a period of two years and 750 stores are selected for each data collection period or wave. A store can only be selected once and if it refuses to participate it is not back into the pool of available stores.

[Slide]

Results--the results of the survey demonstrate a very high rate of compliance, that is, the appearance of a qualification sticker on an Accutane prescription throughout the survey period. The secondary objectives of correctness and completeness were also consistently above 90 percent. This was true for the audit as well.

Results were consistent across age, gender and payer type. Although there were some differences between rural and urban stores and pharmacies with high versus low prescription volume, both high volume and rural pharmacies were more likely to receive prescriptions with incomplete qualification stickers.

[Slide]

I will now discuss selected methodological issues with the PCS first based on results of the pilot study at least 450 stores or 60 percent of the sample needed to respond during each data collection period to ensure an adequate sample for study power. The observed response rates for the first five survey waves ranged from 25 percent to 59 percent.

Second, during the third survey wave five major retail pharmacy chains asked and were removed from the survey pool. These chains represent approximately 33 percent of all retail pharmacies in the U.S. However, they may process more than 33 percent of all Accutane prescriptions.

[Slide]

Finally, based on the pilot study and available data the sponsor estimated pharmacies would have an average of 2.55 Accutane prescriptions for each survey wave. If 60 percent of the pharmacies responded, this would yield 1,150 prescriptions available for analysis. However, overall the responding pharmacies averaged less than one prescription per pharmacy, with an average of 268 prescriptions selected for analysis for each survey wave. Thus, the actual number of prescriptions captured was much lower than expected.

[Slide]

In addition to the main survey, the PCS includes an audit component in which copies of Accutane brand isotretinoin prescriptions are obtained from 15 percent of PCS participants for purposes of comparison. While the actual recruiting process is not described for us, the audit does not appear to be a random sample. Without more detail on the audit the utility and/or

applicability of the audit results is questionable.

[Slide]

In conclusion, the PCS reported a high rate of compliance with qualification stickers. This was seen across all survey waves for both the survey and the audit. Again, it should be noted that qualification stickers are just one component of the current RMP, in this case the S.M.A.R.T. program which incorporated many changes.

[Slide]

The PCS did not realize sufficient sample size or power to definitively address generalizability of the results. Several factors contributed to this, including a lower than expected response from pharmacies; low number of prescriptions captured; and the loss of the five largest pharmacy chains in the U.S. These problems suggest alternate study designs should be considered for future studies with similar goals.

[Slide]

I will now turn to the subject of isotretinoin patient surveys. This section, as

outlined on this slide, will include review of the purpose of the patient survey; its methods and limitations; the survey population and its generalizability to the population of female isotretinoin users at large; the results of FDA analyses; and summary conclusions. To repeat, I will utilize the expression current RMP to refer to the risk management program for isotretinoin implemented as of April 1, 2002.

[Slide]

Purpose--patient surveys were implemented in 1989 in order to assess the compliance of physicians and patients with the Accutane Pregnancy Prevention Program and to identify the rate of pregnancy during treatment with isotretinoin. The sole isotretinoin patient survey up until the fall of 2002 was administered by the Slone Epidemiology Group from Boston University, and is often referred to as the Slone survey. In the fall of 2002 the sponsor of Accutane brand isotretinoin shifted conduct of patient surveys for Accutane from Slone to another provider, Degge/SI.

[Slide]

Data available for this FDA review included review of the Slone Epidemiology Group quarterly reports for the year prior to implementation of the current RMP and continuing into the year following initiation of the current RMP, and primary independent analysis of an Accutane brand patient survey data set, conducted by Degge/SI, for the Accutane sponsor started in the third quarter following implementation of the current RMP.

[Slide]

In order to address revisions included in the current RMP, patients enrolled in the Degge/SI survey received a new survey instrument. To review, the old survey instrument did not ask about the presence of a qualification sticker; did not ask about the presence of a MedGuide; and asked only if any pregnancy test had been performed.

[Slide]

In contrast, the new survey instrument included questions about both the qualification

sticker and the date and number of pregnancy tests performed. The new survey was introduced first to Accutane recipients participating in the Degge/SI survey but not until the third quarter of the first year of the current RMP. Degge/SI would enroll some 6,000 participants through the end of that first year.

[Slide]

Now I would like to discuss some limitations of the survey. The survey is a self-administered mailed survey which would be the preferred method to gather information on sensitive questions. However, this advantage is compromised by the fact that this is not an anonymous survey because it is a follow-up survey. Historically, the isotretinoin patient survey has suffered from low enrollment. Furthermore, low enrollment, in combination with the voluntary nature of the survey, increases the likelihood that patients participating in the surveys may be different in important compliance behaviors than those who do not participate in the surveys.

[Slide]

A further area of concern is measurement errors. These would include recall bias since we are relying on patient memory to recall the exact dates of such events, menses, receipt of a prescription and start of therapy. As highlighted on the previous slide, the lack of anonymity in this survey increases the possibility of social desirability bias to sensitive questions, such as those regarding sexual behavior, birth control use and accidental pregnancy. FDA review also concluded the survey instrument included both complex questions and complex question skip patterns that might be confusing to some participants. In sum, these biases reduce the generalizability or inference of the results.

[Slide]

With these concerns noted, I will now move on to selected FDA results. First, based on FDA analysis, absolute participation in isotretinoin patient surveys, including both the Degge/SI and Slone epi. group surveys, increased from a range of

16 percent to 19 percent in the year prior to implementation of the current RMP to a range of 22 percent to 26 percent in the first year following implementation of the current RMP.

[Slide]

These data are shown graphically on this slide. Note that the X axis is labeled as quarters one through eight, representing the four quarters before implementation of the revised RMP, which was in April of 2002, shown here by this arrow, and the following four quarters. As shown, enrollment appears to have started to increase before implementation of the S.M.A.R.T. program and has either peaked or is increasing very slowly.

[Slide]

FDA was also able to compare two demographic characteristics of patients enrolling in the Degge/SI cohort to isotretinoin recipients managed by AdvancePCS and appearing within the IMS National Disease and Therapeutic Index, on NDTI. As shown in this slide, which is from the ODS review, in comparison to females within both

AdvancePCS and NDTI, it appears that the youngest recipients of isotretinoin, shown by this row right here, are under-represented in the Degge/SI cohort. So, we are comparing 35 percent in the Degge/SI cohort to 43 percent and 45 percent, which you would expect--with the reciprocal increase or over-representation of participants aged 20-29, which is this row right here, so 30 to 28 to 38.

[Slide]

In addition, FDA analyses of the Degge/SI cohort 94 percent of participants indicated that the prescriber was a dermatologist. In comparison, approximately 80 percent of recent isotretinoin prescriptions were associated with a dermatologist. Thus, it appears that survey participants receiving care from non-dermatologists are slightly under-represented within the population participating in the Degge/SI survey.

I will now turn from issues of generalizability and representativeness to apparent adherence with current labeling, first around the initiation of isotretinoin therapy and then, more

briefly, during isotretinoin.

[Slide]

The current isotretinoin RMP requires women to sign two consent forms, one required of all patients and the other required only of females. In FDA analysis of the Degge/SI cohort 76 percent of participants reported signing two consent forms. Four percent signed only one form; 9 percent reported signing no consent forms; and 11 percent were uncertain or did not answer the question.

[Slide]

As noted before, the current isotretinoin RMP requires all isotretinoin prescriptions to carry a qualification sticker. In FDA analyses of the Degge/SI cohort 92 percent of participants reported their prescription to carry a qualification sticker. This is consistent with the findings in the PCS. Additionally, 2.5 percent of participants reported no sticker and 5.5 percent did not know or did not answer the question.

[Slide]

The current RMP also requires women to have two pregnancy tests before initiation of therapy. In FDA analyses of apparently fertile, 15-45 year-old participants in the Degge/SI cohort 91 percent reported at least one pregnancy test; 66 percent reported two pregnancy tests. Performance increased only slightly to 92 percent and 68 percent with restriction to sexually active participants. Participation decreases slightly, to 89 percent and 63 percent, with restriction to participants who reported no current sexual activity.

[Slide]

Review data reported by the Slone Epidemiology Group suggests that the rate of any pregnancy testing prior to initiation of therapy with isotretinoin increased from a range of 77 percent to 85 percent for the year prior to the implementation of the current RMP to 91 percent to 92 percent in the first year of the current RMP.

[Slide]

These data are shown graphically on this

slide which highlights that the improvement began to take place shortly before implementation of the current RMP, shown here again by the arrow, April of 2002, and appears to have plateau'd.

[Slide]

According to the revised labeling, sexually active women receiving isotretinoin should use two forms of birth control, consisting of one primary and one secondary method. In FDA analyses of the currently fertile and sexually active women within the Degge/SI cohort, 95 percent reported use of some form of birth control. Almost 50 percent reported use of appropriate birth control, consisting of one primary and one secondary method.

[Slide]

I would like to highlight that the women included in the previous slide represent only a minority of patients within the patient survey as this analysis was restricted to sexually active women. As outlined in the review, there were in total some 5,300 women who started treatment with Accutane in the Degge/SI cohort. About 600 women,

or 11 percent, reported reproductive state or postmenopausal status post hysterectomy or were of age less than 15 years of age or greater than 45 years. These women were excluded from most analyses for pregnancy specific behaviors. Of the remaining 4,596 apparently fertile women, only 1,806, or 39 percent, reported current sexual activity. The remainder, or 61 percent, denied current sexual activity. If a woman does not consider herself sexually active and that represents the majority of women within this survey, these women may not be prepared for contraception should the need arise.

[Slide]

I will now outline selected FDA bivariate analyses conducted to address the relationship between the presence or absence of a qualification sticker and any pregnancy testing and any birth control.

[Slide]

This table outlines the relationship between qualification sticker and pregnancy testing

based on FDA analyses of the Degge/SI cohort. As can be seen in this table, the overall effect of the qualification sticker did not appear to relate to performance of a pregnancy test as testing was high both in the presence and absence of a qualification sticker. Of particular interest, 9 percent of issued qualification stickers were, by patient reports, not linked to a pregnancy test.

[Slide]

Per the current RMP, the qualification sticker is intended to document that the patient received education and counseling on pregnancy prevention. This table outlines the relationship between qualification sticker and any birth control based on FDA analyses of apparently fertile, sexually active, 15-45 year-old Degge/SI participants. You will note that the N falls--it was about 4,000 in the last table--to 1,788 in this analysis as it is restricted to sexually active women. As was appreciated in the previous slide, there does not appear to be a strong relationship between the presence of a qualification sticker and

compliance with birth control. Birth control use was high among the strata reporting current sexual activity regardless of quality of life sticker. This table also highlights that around 3 percent of apparently fertile and sexually active participants deny the use of any form of birth control.

[Slide]

FDA also has data on participants in the Degge/SI cohort during therapy with isotretinoin. In contrast to the previous slides which centered on reports from around the initiation of therapy, these data are generally consistent with results seen early in therapy with isotretinoin but also may show some signs of complacency. For example, report of a qualification sticker falls from 97 percent around initiation of therapy to 95 percent during therapy. Monthly pregnancy testing also falls from around 92 percent around initiation of therapy to 81 percent during therapy.

[Slide]

Review of data reported by the Slone Epidemiology Group suggests that the rate of any

pregnancy testing during therapy with isotretinoin increased from about 70 percent in the year before implementation of the current RMP to around 85 percent in the first year of the current RMP.

[Slide]

These data are shown graphically in this slide which suggests that the improvement appears to have taken place shortly before implementation of the current RMP, again as noted by the arrow, and thereafter appears to have plateau'd.

[Slide]

The Degge/SI cohort of Accutane users includes 15 reports of pregnancy among 4,277 first-time isotretinoin users. This translates to a rate of 3.5/1,000, which is very similar to the historic rate reported for participants in the Slone survey of Accutane users. It should be noted that this rate is censored and so could be an underestimate of the true rate for this cohort, calculated when all these women finished their course of isotretinoin therapy.

[Slide]

In addition to data by supplied by the Accutane sponsor, FDA has received individual quarterly reports from sponsors of generic isotretinoin and quarterly reports from the Slone epi. group on patients enrolling from one of the three generic brands of isotretinoin. These data, including quarterly reports for the second quarter of 2003 and the third quarter of 2003, are generally supportive of results for the interval of April 1, 2002 through March 31, 2003. Specifically, reported any pregnancy testing prior to initiation of therapy continues at about 90 percent. Report of two or more pregnancy tests prior to initiation of therapy continues at about 65 percent. Report of no birth control among apparently fertile, sexually active respondents continues at about 3 percent; and reports of any pregnancy testing during therapy continues at about 82 percent.

[Slide]

To summarize the findings from both my presentation and the presentation by Dr. Pitts,

isotretinoin-exposed pregnancies continued to occur after implementation of the current RMP. Enrollment in isotretinoin patient surveys increased only modestly after implementation of the current RMP.

[Slide]

Despite their wide utilization, qualification stickers have been issued to patients who have not undergone pregnancy testing.

[Slide]

Lastly, the observed pregnancy rate for the Degge/SI cohort recruited following implementation of the current RMP appears similar to that reported for cohorts recruited before implementation of the current RMP.

That concludes my presentation.

DR. GROSS: Thank you very much. We have a few minutes for questions. I am going to ask one myself. The irrationality of human behavior always intrigues me. Is there any information as to why women didn't get regular pregnancy tests or why they didn't use two contraception measures when so

advised? Do any of the FDA or Slone surveys approach those questions?

DR. BRINKER: I will personally defer that question to another member of the FDA staff if they want to comment on it. That wasn't necessarily included in our review.

DR. TRONTELL: FDA uses the voluntary information that has been supplied--I see Dr. Pitts at the microphone; she can say if any of that was mentioned in the reports that came through the spontaneous reporting system.

DR. PITTS: Actually, I was going to say that, no, the spontaneous reports really don't guide the person in providing the type of information that we wanted for this particular analysis so I don't have any further information. It is somewhat incomplete in that respect.

DR. GROSS: Yes, the only reason I asked is if we are going to be designing new programs or making recommendations it would help to have that kind of information. We have some questions from earlier. Dr. Katz?

DR. KATZ: The data that we are hearing now of people having two pregnancy tests or one pregnancy test or pregnancy tests through therapy, that data is derived from patient recall on the survey? Is that correct?

[Dr. Brinker nods]

Well, that has to be considered seriously because when they are asked that on this very complicated survey that they have gotten from the enrollment, many patients--a lot is going on in their life, in real life, and when you ask did you have a pregnancy test many patients would say, no, I don't remember a pregnancy test, be it a urine test or a pelvic examination. They forget that the blood test includes a CBC, hepatic profile, lipids and, by the way, a pregnancy test. Now, they have been told that at the beginning but all they may know, I would imagine, is they got a couple of blood tests--yes, the doctor gets a blood test every month but they didn't get any pregnancy test. So, that has to be considered in that response, that human response.

DR. BRINKER: I would admit that this is a very blunt tool and the data are what the data are.

DR. KATZ: As a follow-up, was any attempt made by the company or FDA for the patients who said, no, they didn't get any pregnancy test to get follow-up from the doctor's office? That would be relatively simple in a very small pilot manner, and you might find that 98 percent or 100 percent of those people not getting a pregnancy test did get two pregnancy tests and got pregnancy tests every month.

DR. PITTS: In the spontaneous reports there was a significant number of reports that didn't mention the data at all. Of the ones that specifically said they did not get pregnancy tests, we took that as affirmative, that they truly did not get it. Of the ones that mentioned that they received some pregnancy testing throughout, we took that and that is the data that we had to work with in the spontaneous reports.

DR. GROSS: Thank you. Dr. Gardner?

DR. GARDNER: I have a question for each

of you. Dr. Brinker, could you clarify for me, you had said in your PCS results slide, the prescription compliance survey, that both high volume and rural pharmacies were more likely to receive prescriptions with incomplete stickers. Doesn't your methodology look at prescriptions after dispensing has happened?

DR. BRINKER: I am going to defer that question to the primary ODS FDA reviewer of the PCS, Dr. Cynthia Kornegay.

DR. GARDNER: My question then to Dr. Kornegay is does this imply that high volume rural pharmacies went ahead and dispensed in the face of prescriptions with incomplete stickers?

DR. KORNEGAY: No, it does not. This is merely what the pharmacy received. There were other aspects of the pharmacy compliance survey that did point out how many prescriptions were received but not dispensed and that was consistently fairly low.

DR. GARDNER: Thanks. My other question for Dr. Pitts is in using the AdvancePCS data, back

to the issue of labeling compliance that we have talked about several times today, using that database resource, has there been any effort to determine what proportion of people getting Accutane had actually had, and presumably failed, other dermatology therapies before?

DR. PITTS: I am going to defer that to Dr. Mendelsohn.

DR. MENDELSOHN: That was actually one thing that we did not work at, but it would be possible actually to examine that with the AdvancePCS data but we didn't consider that yet.

DR. KWEDER: I believe the Slone unit did address that in one of Dr. Mitchell's backup slides.

DR. MITCHELL: I don't know who said that but thank you. If we could go to my presentation, if that is possible--is it still booted up there?

[Slide]

The survey asked from the outset of the onset of therapy about past treatments. The implication, of course is that these are failures.

One could argue that I suppose. I can't read it from here but I think it is 93 percent that reported that they had previously been on an antibiotic 51 percent, on Ortho-Tricylen or vitamin A 10 percent, Retin-A 68 percent and so forth, benzoyl peroxide and so forth. So a substantial proportion of women have tried one or more therapies prior to Accutane.

DR. GARDNER: For the survey? Thanks.

DR. GROSS: Dr. Honein?

DR. HONEIN: Yes, my question is for Dr. Brinker. When you were calculating the survey participation rate for the first year of the current risk management program were you able to eliminate duplicate enrollments, meaning women that may have enrolled in both the Slone Accutane survey and the Degge Accutane survey?

DR. BRINKER: Well, remember, that only kicked in during the last two quarters so that is the only place that it is impacted, and we took our numerator data from the sponsor. So, if the sponsor would like to elaborate, we used the same

numerator that they used in their. So, to the extent that they were able to do it, we did it.

DR. GROSS: Dr. Epps will ask the last question.

DR. EPPS: My question is for Dr. Pitts regarding the utilization. The percentage of refills with the current RMP fell to 2.4 percent. That seems really low. I was wondering whether a change in the dose was considered a new prescription or was it considered a refill because the patient was continuing on therapy. Sometimes when prescribing Accutane you may start at one dose and modify your dose depending upon blood tests, participant interactions or something of that sort.

DR. PITTS: Actually, as of the implementation of the program all isotretinoin prescriptions are considered new prescriptions. Previously you could write a prescription that was one, plus three refills, and every one is a new prescription. Therefore, the numbers should decrease and approach zero at some point, or at least decrease. When you look at that particular

aspect you should not have refills.

DR. GROSS: Thank you. The next speaker is Dr. Richard Wagner, Kaiser Permanente Drug Use Management.

Kaiser Presentation

DR. WAGNER: Good afternoon.

[Slide]

I am from California. I am here with a colleague of mine, Craig Cheetham, who is in the back, who has helped me put this presentation together. What we would like to do is actually show our results for the past two years. We have actually managed Accutane this year's pregnancies differently than the S.M.A.R.T. program. So, we are going to, for the first time actually publicly, lay this information out for folks to see. We would be interested in your feedback on what things we could do together with the agency or others to work to actually maybe even further validate the results that we are going to present today.

[Slide]

For us it really boils down to the

previous advisory panel from about year 2000 saying that no one should begin isotretinoin therapy if pregnant and that no pregnancy should occur while on that therapy. To me that is very simple, that goal was zero.

Our charge in our organization was could we actually prove that we could get that to zero and prove that it is zero based on a program that we conceived to be different than the S.M.A.R.T. program. Some of you have seen the KP Med-SMART logo. We also got a little bit clever and Med-SMART for us really talks about systematic monitoring and assessment for risk of toxicity. This program could work not only for Accutane; it could actually work for other drugs and we are in the process of figuring out how we are going to add methotrexate into an equivalent program because, if women on isotretinoin deserve to be protected, women who are on methotrexate certainly deserve to be protected also. So, we would like to come back at a future time and let you know how we are doing with that one.

The "how"--the linkage is dispensing of isotretinoin for female patients to verification of a negative pregnancy test. To us it was simple. The pharmacist had to see, either electronically or via paper or some other documented communication, that for that prescription for that woman that day there was a negative pregnancy test before we dispensed that prescription, and we needed to do that every time for every woman in every situation that we manage.

We developed a centralized female patient registry with prescription level detail and associated prescriber and pharmacy performance reporting. You can't put together a program and not report on people's performance. If you don't report, they won't improve or they won't improve very much. Even the best people who will try need reporting and feedback in order to improve. I am going to show you how we do that.

We developed operational guidelines. We needed to have a consistent approach over 250 Kaiser outpatient pharmacies so we wanted to have a

consistent approach and have written operational guidelines for how we do this in each of our pharmacies. We do allow for some reinvention, and I will talk about that later on, because there is always some minor variation that is not going to quite work if you tell everybody they have to do it the exact same way everywhere. But the goal always has to be that nobody gets a prescription for Accutane that is pregnant, or we are not going to dispense an Accutane prescription if we don't have that negative pregnancy test. The patient will have to go get a negative pregnancy test before we dispense that prescription.

We have over 100 dermatologists that we work with in southern California and northern California, and there are guidelines for the appropriate use of Accutane, isotretinoin. Those guidelines have actually been in place for years and over time we have adjusted those guidelines to reflect current reality. So, we actually have a living document that says this is how we think Accutane or isotretinoin should be used in our

program for our patients.

[Slide]

I will only give you one Kaiser slide. Typically the Kaiser folks show up with ten slides because we have a very complicated organization. But in California we take care of about 6.1 million Californians. We are an integrated healthcare delivery system. I am not up here talking about us being a PBM or an insurance company or any of that other type of stuff. We really take care of patients and we do that in a variety of ways. We are linked financially; we are linked operationally; we are linked technologically; and maybe most importantly, we are linked culturally. These efforts within Kaiser Permanente are common efforts for us so I am talking about one example. If we were actually talking about many topics we could come up with many examples of how this approach actually works to provide, I think, very good patient care.

As you know, Kaiser Foundation Hospitals and Kaiser Foundation Health Plan is a non-profit

community benefit organization. In California we work with two very large medical groups, one in northern California and one in southern California. They are an independent group of physicians that contract exclusively to provide care to Kaiser members. In contrast maybe to folks who live in the Washington, D.C./Baltimore area, California is really a hospital-based integrated healthcare delivery system. We have about 29 hospitals and medical centers associated with those hospitals, over 200 medical officers and over 250 outpatient pharmacies.

So, the picture I am trying to paint for you is that you really have to see that laboratories, pharmacies, physicians--everybody is in the same building. I mean people work together. They are busy doing their own things, certainly, but it is a big advantage to actually know people in your building that are taking care of patients and have those folks interact with you to make sure that we can actually take care of patients that require this little bit of extra effort, the best

that we can.

In terms of prescription volume, we have about 42 million outpatient prescriptions. Last year about 24,000 of them were isotretinoin prescriptions. That is pretty consistent, about 2,000 prescriptions per month.

What we don't have in California but other Kaiser regions do have--and it is going to come--we don't have an automated medical record. That is an important thing to keep in mind. When the automated medical record comes-- little pieces of paper with drug names, putting little stickers on them, it is just not going to make it. There has to be a different way involving technology that is going to support the equivalent, and that is ensuring that patients are not pregnant when they get these medications. We don't have that here. One of the advantages in us trying to perfect this process outside of the yellow sticker is that we wanted to learn how to do this so that when the electronic health record comes, the automated health record, we are going to incorporate that

learning into that tool.

The last thing, let me make a connection--and I didn't quite figure this out initially either--we have extensive experience in care management or disease management registries--diabetes, asthma, whatever you want to call it. These are patients at risk also and some of these registries that we manage have over 300,000, 400,000, 500,000 patients in the registries. If you think of the female patient as an at-risk population taking an at-risk drug, many of the learnings from that group are translated into some of the efforts that we are presenting today. So, what we are doing for the isotretinoin patients really is reflective of what we are doing for other at-risk populations.

[Slide]

Some descriptive statistics--we do have IRB approval from southern California to share some of the descriptive statistics. I will tell you that the north and the south are very similar. If we were to do further work with the agency or

others, we could go back and get IRB approval for northern California data also. But it is actually interesting I think the results are somewhat similar to what we have seen today.

This is January, 2002 through November, 2003 data reflected up here. The average age for the female patients is about 25 years. It is about 49 percent females. Unique patients in the south, 2,376; unique patients in north California, 2,253. You can see the prescription counts for those patients. In about 85 percent to 90 percent of the time we can find an acne-related diagnosis in our machine. The other 10 percent just might not be findable or someone didn't code it right. It is interesting to note that cancer diagnosis comes up about half percent and we do have a small number of patients with various cancers that we do treat with isotretinoin.

Another interesting observation is about prior therapy within the previous 6 months, and 95 percent of the patients had not been on isotretinoin before; only 5 percent had had a

previous episode of therapy in the previous 6 months in our program. The range of prescriptions was 1-16, with a mean of 4; 4-5 prescriptions, 30-day supply. It all adds up to about 124 days of therapy per patient. The type of therapies that the patients had before they started isotretinoin are listed there also. About 64 percent of the patients had one of those therapies listed down below. Most patients are not started on isotretinoin as a first-line therapy.

[Slide]

Here is where the good stuff is. It may be a little bit hard to see. January, 2002 through December, 2003, what was going on here? This is before the formal program started, the first four months of 2002. We went back and just measured what was going on in our system during that time frame. I did not do any chart reviews or anything like that, just data system stuff. You can see that about 50 percent or 60 percent of the time we were at baseline compliant with a patient picking up their isotretinoin prescription within seven

days.

Part of that is misleading though because what was happening is that we didn't have all the pregnancy tests in the machine. The dermatologist practice was to do about half of those pregnancy tests in their office, and the big change we had with the dermatologists was saying we have to get you to do these tests so the electronic system can pick them up, otherwise you can't get credit for doing this. If one medical center does it one way and another medical center does it another way we really don't know what is going on. So, the big change we asked of the dermatologists was that at least one test for every dispensed prescription needs to come through the laboratory system because we and the pharmacy can then, from a technology standpoint, see the results of that test. If you test them in the office, that gets put in the chart and we may or may not see it and it won't get reported as being compliant. One of the things we wanted to be able to demonstrate is, if we are going to do something different than the S.M.A.R.T.

program, we want it to be at least as good or better than the S.M.A.R.T. program, and that meant that we had to be able to collect and show data like we are doing today.

So, I don't want to leave anybody with the misunderstanding that somehow the dermatologists weren't doing the right things. I just did not go back to their charts and pull out of all of those urine or lab tests that were in the charts for years and years because that is how they practiced.

But let's look after April. After April, you can see that things got better. We went from 50 percent or 60 percent to about 75 percent or 80 percent. I have to tell you, we went back again and said 75 percent or 80 percent, guys, is just not going to make it either. We have to do better on that one also. So, what did we do? I am going to show you some pictures of this in a minute. We actually developed a web-based tool that was the centralized patient registry. That tool collects every prescription for Accutane for female patients and all of the associated lab values and makes it

available within near real-time back to the medical center so that they can actually act on any discrepancies or make any corrections, if necessary or, if there is a quality problem, actually intervene and try and fix it or get it into the quality system.

So, this web-based tool, and I will show you some screen shots, actually turned out to be the next strategy that we added in here. We were doing this early stuff by reporting, sending pieces of paper out to people and saying please look at this report and please do better. But they did go out two or three months late and, anyone who is involved in taking care of patients and getting a report two or three months late--it means nothing. You have to get a report about performance in terms of patient care within days or maybe a week, otherwise you just don't remember and you are off to the next thing.

So, what happened, lo and behold, we had to go through a little bit of training. We actually did this in the 29 medical centers across

the state and we rolled the web-based tool out about here. When you start providing people with the necessary information and the reporting and the technology to support good clinical practice, and they can see how they practice over time and they can see how their peers and other medical centers practice, the A students go right to the top. That has been sustained now for over a year.

I am going to show you what that tool looks like but the thing that really drove us from mid-level performance to I think pretty high performance was the implementation of the tool in addition to all the other things that we did. The tool by itself wouldn't do it. Without guidelines by the dermatologists and their interest in following up, I don't think we would get there; without the pharmacists paying active attention and just being very rigorous--if you don't have a negative pregnancy test, you have to have it before we fill out that prescription. You start to put those elements together, get people the reporting and feedback they need and they do perform.

I am going to show you that it also worked this way in northern California. This is a different group of physicians. I mean, the physicians in the south and north are really two separate medical groups but the impact was the same.

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I should have made it green or blue or something different but, again, you can see the kind of baseline performance before. This is really written policies, procedures and standards on how we wanted people to behave. In order to really take it from this 80 percent thing, we had to put the same electronic web-based tool in place and, again, provide people real-time information, and we said if you are lagging on performance everybody can see it; you can see it. How are we going to fix it? And, people tend to fix those things as quickly as they can, to tell you the truth.

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A couple of things about pharmacy

utilization, we didn't see a drop in pharmacy utilization within our program. It was very fascinating to me that outside of Kaiser utilization dropped 23 percent or so. We didn't see a change in utilization.

There are a couple of interesting things here. This is southern California data, 2002 to 2003. So, the time frames are not quite matched but, in essence, we are filling the same number of prescriptions this year and last year as we filled in 2002. I really go back to my comments about the dermatologist practice and evidence-based medicine and having guidelines that they endorse. That didn't change with all the things we did when we added our new technology and our new ability to collect and analyze information. I think the practice stayed the same. The one practice element that changed really was to stop doing lab tests in the medical office because we can't track those things. It was just one of those things that had to change. But in terms of I think prescribing to the appropriate people, we did not see a change

really in prescribing for the appropriate patients for Accutane, if you really believe in evidence-based medicine and using the guidelines to drive clinical performance.

It is interesting that there does seem to be some seasonality. I saw some discussion in some of the documents about is there seasonality or is there not. I would say there is seasonality. It looks like this is when kids are in school. It looks like this is when they are at the beach. I don't know if it has to do with the school or the beach or fun, or maybe dermatologists take vacation during the summer, but something is going on there. It is actually very consistent with other pharmacy utilization pictures. Things tend to peak in the wintertime and things tend to drop in the summertime.

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Northern California had a similar pattern. You can see that in 2003 we were actually filling more prescriptions for isotretinoin than in the previous year, but the patterns are very much the

same. So, we didn't see the drop-off in terms of utilization. In fact, if anything, we are filling a few more prescriptions here.

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Let me talk about the web-based application just because I know there is interest in maybe a centralized repository or patient registry for patients. I will say again that basically I really built this in concert with folks who have been managing patients with diabetes, asthma, heart failure, etc. We have extensive experience in terms of managing large patient databases and then using the databases to improve performance. So, we are really standing on the shoulders of others that have come before us.

This is an at-risk population. They may be only at risk for four or five months but the consequences are severe. If it is really the goal to have nobody become pregnant while on this medication, then you need to have tools similar to this I think to be successful.

It acts as a centralized patient registry.

It is indexed on an isotretinoin prescription. So, we only know about you if you got a prescription filled in our Kaiser pharmacy. There are some problems a little bit with that too, but 95 percent of our patients have Kaiser drug benefits so we are probably picking up at least 95 percent of those prescriptions. Prescriptions can go out of the system and we would lose them in that case. Prescriptions can come into the system and we would add them in also.

The system automatically links pharmacy, laboratory and patient demographic data. We refresh it weekly. We could refresh it daily but we expect people to take a look at the tool weekly because that is usually soon enough for us. The other aspect of the tool is that 93 percent of the time we pull the data in for the people. There are folks in the medical centers, pharmacists and dermatologists and nurses that are taking care of patients and you don't want them having to type data in the machines. Seven percent of the time there is a transactional input because we still

honor the yellow sticker. So, to the degree we have a manual prescription without the laboratory coming through the Kaiser system, we will honor that prescription whether it is from a KP dermatologist or someone outside. So, about seven percent of the time we have to type that thing in. You know, that is a bit of a pain but that is how you get credit. If you don't type it in I will see a gap in your performance and they will get a phone call.

What is also important here--we do this with every other tool that we have, we compare medical center performance to medical center performance during the same time frame, and we also tell our medical centers to compare their performance over time. It is up to each medical center to actually get into the nitty-gritty of this stuff. That is where patient care is provided. They have the tools in front of them to see their own performance. They know everybody else sees their performance; they see everybody else's performance and it actually does make people

perform because, first, they always want to do the right thing for the patient but then, if you put up something like this, they absolutely want to do well in terms of the performance that is out there.

Data is current. That is another key thing for us. If data is not current people can't be expected to act or react or to improve. Getting physicians' or pharmacists' or nurses' data six months old means nothing. We download the data into Excel format for custom reporting so if you want to do some custom reports at your medical center, you can actually download that thing and actually create all the funny little reports that you want, and you can actually drill down into the prescription level data, the physician level data, the pharmacy level data, and patient level data and we know everything about everybody and we also can roll it out so that people can see it at a high level also.

Most importantly, security and limited access to protect the confidential nature of this data--it is heavily protected. It is password

protected. People can't get in there. People who do get in there we know about and if anybody, God forbid, does something wrong, you know, they are going to get fired during these days of confidentiality.

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I am going to give you a couple of screen shots and then try to move pretty quickly. Here is a screen shot that I took. It was a screen shot from data refreshed through 2/13/2004. This actually shows you January of 2002 to December, 2003. The essential thing is that we have this web-based system. The data is displayed. People can roll it out and with the tool itself you can actually monitor managed performance.

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I want to finish up with a couple of things. For those of you that read Paul Plsek, these are complex human behavior things. They are not complicated issues. One thing I think the risk management people and maybe the FDA could learn is that people who do population management actually

manage patient care. The difference is between managing a complicated problem and managing a complex problem. I am not going to go through that today but there are people out there who are experts in this area, obviously.

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There are some issues here that kind of differentiate between a complicated problem and a complex problem. I will leave you that to read.

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Another guru here is Don Berwick who has laid out much of what it takes actually to change the healthcare system. If you are not looking at what he has to say in this area, you may be missing an opportunity to truly improve the healthcare system in this country.

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I will finish up with why this is working at Kaiser Permanente. I probably have already convinced you of this, I hope. Physician and pharmacist buy-in. We work as a team. It works because people there are committed. There is a

huge cultural alignment to make this work.

We also allow for reinvention locally. If a lab locally and a pharmacist want to get together a certain way that is slightly different but the pharmacist has that negative pregnancy result before they dispense a prescription, it is allowed. We just want that documentation. You have to have some flexibility to help people work together because things are just not set up exactly the same every place.

I have also talked about technology and data. It is readily available. It is in real time. That is obviously a big advantage. Performance reporting and monitoring is critical to success. People do not get better unless they have real-time performance reporting and monitoring. And, quality issues are reviewed through the normal peer review quality channel at each of our medical centers. In the event that there is a quality issue, that does get channeled normally through for peer review and then the quality process takes hold.

I am going to stop there and take questions, and would be interested if anybody had any observations.

Questions to Kaiser from the Committee

DR. GROSS: Dr. Trontell?

DR. TRONTELL: Yes, with your impressive improvement in pregnancy test performance, I wonder if you can give us any information on differences in pregnancy outcomes, and whether the Kaiser system captures information on contraception use as well as various forms in which pregnancy might be terminated.

DR. WAGNER: Yes, we would have to do some additional work because I pulled most of this data off our systems. But, in theory, we would be able to go back and link this up. In essence, you have a northern and southern California cohort of 5,000 patients during this time frame. For example, what we haven't done is take a look 60 days out after the last fill so that a patient has a prescription, three days worth of medicine and then add 30 more days in and what was their pregnancy status 60 days

after that dispense or 30 days after the last fill? Those are things that we could actually work on because the data is available. We just haven't done that level of work. In theory, we could data mine and find all sorts of things. If we spend some time and effort, I think we can actually tease out much of this.

DR. GROSS: Dr. Kibbe?

DR. KIBBE: The crucial question was asked. Without an endpoint of knowing how many pregnancies occurred in your system, I don't know whether it is any better than anything else.

DR. WAGNER: The one thing we can ascertain looking back at 2003 data, and I have done this myself in addition to the data people, is that we had no patient who was pregnant and received an Accutane prescription in 2003 in northern California and southern California, and we had no patient who was on Accutane and became pregnant during that time frame. Now, we should do a little bit more work because people could become pregnant, like I say, 30 days after and we haven't

picked up that data. We would be willing to look at that also just in the event there was a pregnancy after the last Accutane fill.

DR. GROSS: Dr. Day?

DR. DAY: We all have the same question. Could you just repeat that last part? Are you saying there were no fetal exposures in the initial period and during the period of taking the drug, and you just haven't looked at the 30 days post?

DR. WAGNER: For 2003, north and south, we can find no fetal exposures.

DR. GROSS: Dr. Vega?

DR. VEGA: Yes, I have the same question Dr. Trontell had about the pregnancy occurrence among your group. Have you done studies to link pregnancy status with drug use or pharmacy prescription before?

DR. WAGNER: General studies?

DR. VEGA: Yes.

DR. WAGNER: No. Actually, this was probably more work we have done related to pregnancy status or potential pregnancy status than

any other work we have done.

DR. GROSS: Dr. Wilkerson?

DR. WILKERSON: First of all, my compliments. This is truly what I was talking about before as best of practices and it doesn't get any better than a controlled setting like this. Having been a managed care director myself, I can tell you that trying to get physicians to go in one direction is like herding cats and you certainly have mastered the art, probably from a monetary reward, but it certainly helps change behavior.

This is the sort of stuff that we need as a committee before we go inventing the national wheel to know in best practices does a particular strategy work. If this data holds up--I mean this is an ideal situation. Physicians are controlled. The distribution is controlled. You have a panel of patients that are interested in their health. This is the sort of stuff that we need to know as a committee if we are going to recommend something that is not a band-aid, that in best practices it does work. So, my compliments to you.

DR. GROSS: I would echo that question. Your adaptive complex system works because you have a homogeneous culture. In the rest of the world where medicine is somewhat of a free-for-all, do you have any lessons for those systems, any suggestions? You said you actually publish the results and show them to the doctors as a group so they see everybody else's results.

DR. WAGNER: Yes.

DR. GROSS: What kind of feedback do you get on that? Do they accept that?

DR. WAGNER: Absolutely. It happens all the time, not just with this report but whether you are managing an asthmatic patient or any other groups of patients. Using unblinded peer comparison reports--they are protected from a confidentiality standpoint; I mean, it is in a departmental meeting or that type of thing--is a very powerful tool to get people either to change or, you know, there are times when there may be justifications for a practice but it is a very effective technique that has been used over and

over.

One thing I would add, and I actually just discovered this maybe in the last month, there is a clozapine registry that I think has many of the same elements. The Ivax company in Florida that manufactures clozapine requires white cell counts before you can dispense it. This clozapine registry is an absolutely fascinating tool. It is very similar to our Med-SMART tool in terms of the functionality and capability. So, if anybody is interested in looking at that, and the agency certainly has some review of clozapine--if they could demonstrate similar levels of compliance, because that would be outside of Kaiser Permanente, then that might be a very powerful learning also.

DR. GROSS: Dr. Bigby?

DR. BIGBY: I would like to know what was your experience in terms of numbers and rates of pregnancies on Accutane prior to April of 2002.

DR. WAGNER: I don't have those actual numbers. Those numbers would be rolled up at a medical center level. They would have been dealt

with in the confidential peer review quality assurance process. So, I don't actually have those data. They weren't available before we actually started this program in a centralized fashion.

DR. BIGBY: So, it is possible you didn't have any before.

DR. WAGNER: It is possible we didn't have any before. Again, if you talk to the dermatologists I work with, they will tell you that this whole thing that they are going through they don't think changed quality much. But it actually I think demonstrates quality in a way that if you ask me that question today I actually have a lot greater degree of confidence that, yes, the quality is here. But the dermatologists who do this quality review process would tell you I think they don't think they had much of a problem before.

DR. GROSS: Dr. Whitmore?

DR. WHITMORE: I think your program probably does prevent initiation of Accutane when pregnancy is present. As far as preventing pregnancy during therapy, I would question how you

gather data about pregnancy. I would also say that some women may take abortifactants and never report that to their doctors, and also go outside of your system for an abortion.

DR. WAGNER: Exactly. The program--because it indexes on Accutane prescriptions, at the end it is open. But I think there are enough data elements within our system that we could actually figure out how big a problem, if any, does exist.

DR. GROSS: Thank you very much. The next speaker is Dr. Richard Miller, Professor and Associate Chair of Obstetrics and Gynecology. He will talk about the Organization of Teratology Information Services, and this is an interim report.

Organization of Teratology Information Services, Interim Report, North American Isotretinoin Information and Survey Line

DR. MILLER: I appreciate the opportunity of joining you today and reflect back on my first visit with you all, back in the early '80s and

beyond.

As indicated, I am on the faculty of the University of Rochester but I also am Director of PEDEX, NIH a New York teratogen information services as well. So, I tend to see the patients who do become pregnant and are, in fact, addressing those sorts of issues today.

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What I will be talking about is what OTIS does. How we, in fact, have gotten involved in the Accutane issue, and I will share a couple of cases with you and a study that we have been doing, called the OTIS North American Isotretinoin Information and Survey Line. This is an interim report. We were asked by the FDA to come forward with our data as we are in the middle of this particular study.

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The study is funded by the CDC in partnership with the Association of American Medical Colleges, and you can see the other individuals that are involved with this program.

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OTIS is a non-profit North American network of 19 state or regional teratology information services. These TIS provide updates on information regarding the effects of drugs and chemicals on the human embryo and fetus via a free of charge telephone consultation. There are more than 100,000 calls per year that we receive. Half of them are from the general public and the other half are from healthcare professionals.

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OTIS is organized to stimulate and encourage research, education and the dissemination of knowledge in the field of teratology and, hopefully, to improve the abilities or teratogen information services to provide accurate and timely information about prenatal exposure with the overall objective or preventing birth defects and improving the public health.

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Now, in 2002 we provided testimony to the Subcommittee on Oversight and Investigations of the

Committee of Energy and Commerce of the U.S. House of Representatives. I share here some of the recommendations that we have offered at that time. In brief, OTIS recommended safeguards that are modeled on the thalidomide steps program, which include several mandatory elements.

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OTIS also recommended strict adherence to the approval indications for the use of isotretinoin, limiting prescribing to dermatologists and the S.M.A.R.T. program, improved contraceptive counseling, and direct patient access to risk assessment and counseling and, very importantly, the continued evaluation of the effectiveness of these programs. Because I have limited time, I have highlighted only a few of these recommendations, and down here you can find the entire report, here at the web site.

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We have been active and in 2000 the California Teratogen Information Service contributed to a study of 14 women whose

pregnancies were inadvertently exposed to isotretinoin, reflecting the failure of the Pregnancy Prevention Program.

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At that time, we began cataloguing the number of calls that we get at OTIS across the United States and Canada, and here you can see the numbers that we have gotten over the past three years. This was at the same time that we are now beginning to look at the transition to new systems, the S.M.A.R.T. versus the old pregnancy prevention system. In these particular instances though we have not found, at least in our calls of very specific patients who call in, any decreases in the number of calls that we have been receiving during those times.

In collecting this information, we also realized that we needed to gather much more detailed information from these patients to better understand why they were not successful in preventing pregnancies.

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In so doing, we initiated the isotretinoin survey and, remember, these are women who voluntarily called our service seeking help. So, we spend a lot of time with these patients, counseling them up front and then, at the end, ask them if they are willing to participate in the survey. So, we have already gained some confidence with these women and begin to know them, at least from that first meeting.

There is going to continue to be enrollment through September, 2004, and we use a very detailed and structured interview by a research specialist and the participant is followed until the known outcome of the pregnancy.

Our objectives for this study have been to identify barriers to the successful implementation of the components of the pregnancy risk management programs. Remember, we are talking both about Canada and the U.S.

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As we have seen multiple times, there are two major goals to the S.M.A.R.T. program, one to

prevent pregnancy in women who are already taking isotretinoin and to prevent embryonic exposure to isotretinoin in women who are already pregnant. I would like to share two case examples with you. We have been talking about general specifics, but let's talk about two ladies who called our service.

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I will call our first lady Ms. A. She is a pregnant woman in her 30s and she has reported to us that she had exposure between the third and seventh week of gestation. She reported discontinuing her birth control method one month before starting isotretinoin and misinterpreted her doctor's statement that it might be more difficult to get pregnant for a time afterwards to mean she couldn't get pregnant.

She also reported to her dermatologist that she couldn't get pregnant and, therefore, he took that as a reason not to counsel the patient about contraception or do pregnancy tests. She also was reported to be taking samples of isotretinoin to treat a chronic skin condition that

was not acne. So, she was receiving these from her dermatologist; she didn't have to go to the pharmacy.

So, here we are relying on a variety of information from the patient that led to, obviously, a very serious problem, the fact that she is pregnant and we do not know the fetal status at this point today.

I add as an additional comment that we reviewed the patient's exposure history here because we were not aware that physician samples were available for isotretinoin. All of her responses though were consistent with that.

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Let us turn to Ms. Z. Ms. Z. is a pregnant teenager. She called one of our Teratogen Information Services to learn about potential problems that her baby might have because of isotretinoin exposure that occurred between five and six weeks for a total of about six days. She had never taken isotretinoin before, however, she wanted to clear up her acne. She reported that she

learned she was pregnant following a phone call from her dermatologist.

Because a family member was present when the phone call was received, she reported to her dermatologist that she was not sexually active and that the test must be incorrect. Her dermatologist reportedly accepted her statement and thought the pregnancy test must be incorrect and gave her a prescription for isotretinoin which she started the very next day.

After taking isotretinoin for those six days she decided to have another pregnancy test and when, in fact, she discovered it was positive she stopped her isotretinoin. Her pregnancy is continuing and the fetal status is also unknown.

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So, from these case histories we can see really an illustration of several missed opportunities for prevention of exposure to isotretinoin during pregnancy. The errors arise from multiple sources--miscommunication between the healthcare provider and the patient;

misinterpretation of information by the healthcare provider; and denial of risk by the patient. Lack of adherence to the required components of the risk management program remove safeguards that may have prevented these exposures.

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Let's turn to our study. We have a limited number of cases, a total of 23, half from the United States and half from Canada. There are key differences here because in Canada we continue to have the Pregnancy Prevention Program whereas in the United States we have the S.M.A.R.T. program so we have a built-in comparison, you might say. In Canada 100 percent of the patients were taking Accutane. In the United States 55 percent of the patients were and one patient was actually given both Accutane and a generic.

If we look at some of the data, especially what may be considered why they were taking it, in response to several questionnaires about the use of isotretinoin we asked our patients about whether they were being treated for severe, recalcitrant

nodular acne. What you can see here is that 36 percent of the patients described their skin condition as cystic or nodular in the United States and a similar number in the Pregnancy Prevention Program. Even fewer recalled that their doctor had diagnosed this condition.

Somewhat more encouraging, which in fact was discussed a little earlier, is that 82 percent of the patients were, in fact, previously treated with oral antibiotics; 57 percent in the Pregnancy Prevention Program in Canada.

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So, this helps to establish to some degree what, in fact, was the usage but we were more concerned with the elements of the S.M.A.R.T. program and the survey included questions that explore almost all aspects of women's pregnancy exposure but today I am going to limit it to, and highlight, these four elements. These elements pertain to monitoring for the pregnancy program and they can be objectively evaluated, and are the keystone of an effective prevention program.

If we turn to "women must have two negative pregnancy tests" and, obviously, you are all aware of that what we asked our patients about was whether, in fact, they had a second pregnancy test during their menstrual period before beginning isotretinoin. Interestingly, 27 percent did and 3 percent did. Thus, for the S.M.A.R.T. program alone it appears that 73 percent of the women surveyed were not screened using two pregnancy tests as required by the program. In addition, 22 percent of these women reported that they had one pregnancy test that indicated they were not pregnant when, in fact, they were. A second test might have successfully prevented the exposure.

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Our second element--according to the S.M.A.R.T. program women must use two forms of birth control simultaneously starting one month before receiving the prescription. Overall, 70 percent of the women surveyed said that they were using at least one birth control method and this was similar in the two groups. However, only 36

percent of the women in the U.S. and 8 percent of the women in Canada reported they were using the two forms. Thus, 64 percent of women surveyed indicated they were not following the S.M.A.R.T. requirements to use two forms.

I must add though, in addition, when women who reported they were using contraception one of the responses was referring to unreliable methods such as the rhythm method. This, again, confirms the need for effective contraception counseling.

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Our third element--according to the S.M.A.R.T. program women must receive a pregnancy test each month before refilling their prescription. Only 36 percent of our women in the U.S. reported that they had monthly pregnancy testing during the course of therapy. Actually, the percentage in Canada was much higher. Our conclusion is that it appears that 64 percent of the women in our group were not screened for pregnancy monthly as required.

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Our fourth element--pharmacists must only fill prescriptions that bear a yellow qualification sticker. The responses from our group, and maybe it is an unusual group, are that women who recalled seeing a sticker on their prescription that they took was about 30 percent. For more than two-thirds of the women surveyed there is doubt about compliance with the use of the S.M.A.R.T. yellow prescription program. So, our data set of women, which may be unusual, indicates that these are some of the issues that they believe they noted.

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In response to participation in any of the manufacturer surveys, this is where we were disappointed that about 13 percent of them reported contacting the survey; 65 percent reported they did not participate in any of them and actually 18 percent couldn't be sure, but it is different than the reports that were seen so this may be a subpopulation. This may be due to the new management for the change of the Accutane survey;

dual surveys for brands and generic preparations; and different names and appearances of the risk program as it moved through the process. But we are talking here 13 percent.

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Strengths of our study--these interim results presented here should be considered in light of strengths and limitations. All the staff has extensive experience in communicating with women about their reproductive concerns. This experience was used in designing a survey that elicited information while respecting the difficult issues that these women were facing. The survey used a detailed, structured interview instrument. Most interviews were completed within three months of exposure and before the status of the fetus was known.

Some of the limitations here are obviously the small numbers because it is an interim study. All of our estimates were based on women's recall of events which may have been influenced by a number of factors. Finally, women who call a

Teratogen Information Service and agree to participate in our survey are likely not representative of all women who take isotretinoin, and may not be representative of all women with an isotretinoin exposed pregnancy but obviously we have demonstrated a very unusual population.

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So, our preliminary conclusions indicate that the data collected in our studies of isotretinoin exposure in the U.S. prior to institution of the S.M.A.R.T. system found similar rates of non-compliance with U.S. and Canadian programs. These data illustrate that preventable exposures continue to occur due to non-compliance with current requirements, and that perhaps this survey information will be helpful to you and others as one begins to use this qualitative data to identify risk factors for exposure.

One of the things that really came out to us in this survey is how important the counseling to this group of patients related to contraception and to pregnancy test is so critical. The optional

need or opportunity to refer to a woman's healthcare provider may be one that we need to look at even more closely.

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Before taking questions, I would like to close by saying that the desire for a healthy child is nearly a universal one. OTIS is dedicated to helping women and their doctors in this endeavor and we hope that this OTIS survey will be useful in identifying missed opportunities for preventing exposure to this powerful teratogen during pregnancy.

Finally, as a personal note, one question I would like to raise with everyone around the table here is when we are talking about getting a dermatologist certified and we all are constantly having to go through a recertification processes, but it hasn't been mentioned at all at the table here whether in fact having updates in requiring recertification, reinforced with those that are prescribing, is of importance to what we are doing here today. Thank you, and I am open to questions.

DR. GROSS: Thank you, Dr. Miller. Our first question is from Dr. Epps.

Questions to OTIS from the Committee

DR. EPPS: Yes, we recertify in dermatology, and I can assure you a lot of the things you have addressed as far as continuing education goes on--the American Academy of Dermatology at all of our meetings at the local level, the national level and our publications we talk about this drug; we talk about Accutane all the time.

I would like to ask you, however, there are some other drugs and substances which are associated with embryopathy, everything from TORCH infections, radiation exposure, but specifically medications which include anticonvulsants which are commonly used, also aminopterin and other medications reported. Someone mentioned methotrexate which is definitely a category X medication. Do you all also monitor pregnancy rates with other category X programs? We know about thalidomide; we have talked about that. But

I would counter that, you know, certainly methotrexate is used for juvenile rheumatoid arthritis, as well as some psoriasis and certainly pregnancy potential is there for those patients. Those happen in young people all the time, those conditions, and are we treating this drug equivalently?

DR. MILLER: I think you know the answer to that one, that we are not treating them equivalently. We are treating this drug much more like a thalidomide than we are treating them like a valproic acid or diphenylhydantoin. Perhaps some of the reasons for that can come from the fact that many of these patients are on them chronically and, therefore, someone who is taking an anticonvulsant if, in fact, she is ever going to become pregnant--and for phenytoin we are down around the 10 percent level of the phenytoin syndrome, she may never be able to get off that medication. Obviously, we want to get folks off the valproic acid because of the neural tube defects. This needs to be thought of up front with the healthcare

provider who is prescribing, the neurologist or whoever, and also the obstetrician/gynecologist in her planning for a pregnancy. In those particular instances that is certainly a bit different than what we are talking about here about a rather acute, even though only a five-month, exposure.

DR. EPPS: Also, I don't know if we have mentioned alcohol--

DR. MILLER: Yes, Sidney Wolfe didn't do that this morning. He said the two most critical ones and he left out alcohol. I noticed that too.

DR. EPPS: Fetal alcohol syndrome is certainly a lot more common.

DR. MILLER: Yes.

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

DR. GARDNER: Can we ask the manufacturers to address the question of sampling?

MS. REILLY: Tammy Reilly. We absolutely do not sample isotretinoin. What we do is we have a medical needs program that provides drug for indigent patients. We do that for all of our drugs

at Roche Pharmaceuticals because we feel that any patient who is under-insured or uninsured should have the opportunity to get our drugs. So, I can only surmise that perhaps the sample that this person is referring to might have been through that program. What is required in that program specifically for Accutane, which is different from any other drug that we have and provide at Roche through this program, is that in addition to the form that the physician must fill out to qualify the patient from a financial perspective, we also require that they actually include the sticker on the form that states that they have qualified the patient according to the contraindications and the warnings of the package insert when they send in that form. So, we would not expect that they have not gone through the rigorous process that they would be expected to do through a normal prescription process.

DR. GROSS: Dr. Whitmore?

DR. WHITMORE: Dr. Miller, when you were asking about recertification, did you mean with the

S.M.A.R.T. program?

DR. MILLER: Yes. If you have to do it once, why not do it again?

DR. WHITMORE: You are right, we only do it one time and I agree with you.

DR. GROSS: Dr. Bergfeld?

DR. BERGFELD: Thank you. I just wanted to have addressed somewhat of an inconsistency. If those two cases that you used as illustrations were typical of those who called in and actually reported to you so you could interview them, it is hard for me to imagine that if they were able to do that that they would not have read the information that the physician gave them, signed it and sent it because to make this call is quite a step. So, I see there is inconsistency here in the type of person that we are talking about.

DR. MILLER: Well, I agree wholeheartedly with you that you have a subset of the general population and you are using numbers of 96 percent successful with writing the qualification. I imagine the subset of women we are talking about

here is probably well below one percent of the users of this drug. But these are, at least in this case, 24 women who have, unfortunately, not been successful with the Pregnancy Prevention Program and, for a variety of reasons along these lines, many of them shared with the healthcare professionals in terms of misunderstandings but also problems with not using the right form of contraception. But these are the ones that are falling through the cracks. Obviously, most women are doing well. We are trying to identify what is that population that isn't doing well. This is where we come up with all of these inconsistencies because they are a subset of the total group that is certainly different. I don't know if I answered your question.

DR. BERGFELD: I guess the bottom line is they didn't read the information given to them and shared with them by their physician and then they are smart enough to call your group. There is an inconsistency in that they can understand the directions. Compliance is another thing but

consistency of understanding, and you indicated that they didn't understand.

DR. MILLER: Well, the part that they didn't understand, that was when their OB did a procedure that then said, gee, you probably will have difficulty getting pregnant for the next year. She interpreted that as, well, I can't get pregnant. She passed that on to another healthcare provider who said, well, if you can't get pregnant, then you fall into that group and, therefore, we can give you the drug. So, there was a variety of levels of misinterpretation for that patient. But I agree in general. If they have signed all of these consent forms and have managed to get this far along, they should be able to do better, but this is the nature of that subgroup that is getting pregnant and that is the group we are trying to help.

DR. GROSS: Robyn Shapiro?

DR. SHAPIRO: Along those lines, and I am assuming the answers here, but did you go back and check with the providers about the accuracy of the

report of the patients about what exactly happened?

DR. MILLER: At this point in time we are providing you interim results. We have not contacted any providers at this point and this survey is based upon what women are, in fact, reporting to us. In this particular situation one may defensively point fingers in different directions too.

DR. SHAPIRO: So, do you have plans to do that?

DR. MILLER: As part of this survey we do not have permission at this point to contact the providers and we have contact with the patient. So, this may be a possibility in the future but our IRBs have not approved us to do that, and certainly Paula Knudson would not want us to do that without approval.

DR. GROSS: Thank you all very much. It is time for a break. We will reconvene at 3:15.

[Brief recess]

DR. GROSS: We have two more presentations before we close. You have all had a chance to call

your offices and know what misery greets you on Monday.

[Laughter]

I see a lot of nodding heads. Okay, Dr. Kathleen Uhl, working at the FDA on the pregnancy and labeling team, will talk about risk management options for pregnancy prevention.

Risk Management Options for Pregnancy Prevention

DR. UHL: Thank you and good afternoon.

[Slide]

The goals of this talk are, first, to describe the general principles of what constitutes a teratogen, and then to describe the elements that go into the decision-making process regarding risk management strategies to prevent fetal exposure to a particular drug and, lastly, to describe existing strategies that are used to prevent pregnancy and, therefore, prevent fetal exposure.

[Slide]

For most people, and in very simple terms, a teratogen is an agent or a factor that causes birth defects or congenital malformation. There

are some other definitions that are more scientifically driven. One example is here on the slide, that a teratogen is an agent or factor that causes the production or physical defects or abnormal development in an exposed embryo or fetus. One of the common misconceptions though about the word teratogen is that people think that exposure to the agent or drug will always result in abnormal fetal development.

[Slide]

It is probably more accurate to use the terminology teratogenic exposure as opposed to teratogen. Teratogenic exposure implies that a drug or agent has teratogenic potential at clinically relevant doses that are used in humans. Despite exposure to a particular drug or agent, at the right dose and at the right time in pregnancy, this does not necessarily result in a birth defect so the teratogenic effect is not 100 percent.

[Audio technical difficulty with slide 5 and 6]

... a teratogen is with animal data.

Animal studies are typically performed in the pre-marketing phase of drug development to assess reproductive risk. The animal data are particularly useful for generating signals about whether a drug may be a human teratogen. The assessment is based on the totality of evidence from animal data as well as what is known about drugs with similar pharmacologic activity. If the data are concerning one could conclude that a drug is highly suspected to be a human teratogen. In this case the drug is not yet proven to be a human teratogen. Based on animal data alone we will never be able to conclude that a drug is a human teratogen.

[Slide]

The way that we do that is with human data. Typically, it takes years even decades to generate sufficient human pregnancy exposure data to conclude that a drug is a human teratogen. There are some sources that are very useful in assessing whether or not a particular drug is associated with teratogenicity. These include such

things as adverse event reports, those that are reported to regulatory authorities and the example here would be the MedWatch forms. Case reports, case series, case control studies that are found in the medical literature are very useful. In the case of isotretinoin there were case reports of teratogenicity within the first year of marketing in the U.S.

Another source of information are the data that come from pregnancy exposure registries which are prospective epidemiologic studies or data that can come from other post-marketing studies. The peer reviewed assessments that are done by the Organization of Teratogen Information Services and also by TERIS are typically not independent data sources and they really serve as a resource that helps pull together all the various data sources into one location.

[Slide]

Now what I want to do is move on to discuss how we go about a decision-making process regarding risk management to prevent fetal

exposure.

[Slide]

When developing and implementing pregnancy prevention strategies it is important to match the strategy to the level of concern that you have for that drug. Here we have listed three levels of concern just for simplification purposes. When the data do not indicate fetal risk the level of concern would obviously be quite low. The next level of concern would be when we have animal data or other sources that are very concerning and, in that case, we would consider the drug to be highly suspect to be a teratogen. The highest level of concern is for those products that are known human teratogens.

It is important to keep in mind that not all teratogens are equal and you need to consider the frequency, the severity of adverse fetal outcome, the reversibility and the timing of exposure in the selection of pregnancy prevention strategies.

[Slide]

Another aspect of the decision-making is to understand what is the risk. In order to do that you need to address some specific aspects for fetal risk. For example, the frequency of the event, is the event of high frequency or low as it compares to the background risk for congenital anomalies?

What is the severity of outcome? By regulation, all birth defects are considered serious. However, not all birth defects are equal. For example, there are some birth defects that are incompatible with life. There are other birth defects that are cosmetic. The example of that would be the tooth staining that can occur following exposure to tetracycline. There are other birth defects that are reversible. There are some congenital heart malformations that can be surgically corrected.

The type of abnormality is important to consider, and those were reviewed on a previous slide. The timing of exposure is a critical item to determine in assessing risk. When during

pregnancy is exposure associated with the highest risks to the developing fetus? For example, if a birth defect is associated with first trimester exposure, that actually rather broad range, could the time of exposure be narrowed to a very defined time, for example the ninth to the eleventh week of gestation? Or, as in the case with ACE inhibitors, is the birth defect associated only with second and third trimester exposure? With the ACE inhibitors therapy can be easily discontinued or changed prior to the critical time of exposure for adverse fetal outcomes. The earlier in pregnancy the adverse fetal effects occur, the more likely it is that pregnancy prevention strategies are needed. The severity and the type of adverse fetal outcomes affect our perception of "badness" and help to drive the decision to implement pregnancy prevention strategies.

[Slide]

Another element that goes into the decision-making process is the consideration of maternal disease. Maternal disease itself may

carry increased risk for birth defects. The example that has already been given is that of diabetes. Untreated maternal disease may have serious untoward consequences on the health of the mother or the fetus. An example would be untreated seizure disorders. The benefits of treatment are important. The risk/benefit to the mother and the fetus colors our willingness to accept birth defects or adverse fetal outcomes.

[Slide]

Despite the many drugs that are on the market, there are only a few and some sources say that there approximately 19 drugs or groups of drugs that are believed to be teratogenic in humans. Several of the known human teratogens do not have specific pregnancy prevention strategies.

What I would like to do here is contrast two well-known human teratogens, warfarin and isotretinoin. The toxicity for warfarin is well-known and the warfarin embryopathy has been well characterized. The teratogenic risk is relatively small and occurs at relatively low

rates. The window of exposure for teratogenic risk is highest in the second half of the first trimester and the window is even narrower, six to nine weeks, of fetal life.

Females of childbearing potential represent a small percentage of patients who are taking the drug, and the patient-provider relationship is typically more comprehensive owing to the long-term treatment of chronic medical conditions such as continued anti-coagulation for artificial heart valves or for thromboembolic disorders.

With isotretinoin some of the toxicity is well-known, in particular the structural malformations are well-known. There are other toxicities that are not as well recognized. The risk is larger and occurs at higher rates. The window of exposure is highest in very early pregnancy and some have estimated that the highest risk period is from three to five weeks. The overall use of isotretinoin is high in females of childbearing potential and the patient-provider

relationship is of relatively short duration and targeted to a single medical problem, that being acne.

[Slide]

There is no question and we are not debating whether isotretinoin is a human teratogen. There are multiple developmental abnormalities that are associated with isotretinoin exposure to the developing fetus. As illustrated here, there are multiple structural malformations including craniofacial and ear findings. It is estimated that the full spectrum of retinoid embryopathy occurs in 20-30 percent of exposed fetuses, as was mentioned earlier this morning by Dr. Lindstrom.

However, it is believed that even higher numbers of exposed fetuses have single structural malformations. The work done by Adams and Lammer in the early '90s demonstrated a high incidence of intellectual deficits in children who were exposed early in the first trimester. The intellectual deficits were found in children both with and without major structural malformations.

Another developmental abnormality that is associated with teratogenicity in general is fetal and infant mortality, and isotretinoin is associated with increased spontaneous abortion and premature birth.

The critical period of exposure is very early in gestation and is reported to be from the 28th to the 70th day of fetal development, with the most critical time being the third to fifth week. It is important to note though that no apparent relationship has been found between the duration of exposure and resulting malformations. Teratogenic outcomes consistent with retinoids have occurred following only one dose of isotretinoin during pregnancy.

Isotretinoin has unique pharmacokinetics. The half-life of isotretinoin and its major metabolite are approximately 24 hours. So, even with immediate cessation of drug it will take approximately two weeks for 99 percent of the drug and metabolite to be cleared from the body. It is important to remember that stopping the drug does

not result in immediate cessation of exposure to the fetus.

[Slide]

To reiterate--as if we haven't seen this slide enough times--the goals of pregnancy prevention are that pregnant women do not receive the drug and that females of childbearing potential do not get pregnant while taking the drug. In addition, this second goal would also encompass the 30-day period after drug has been stopped.

[Slide]

For products for which there is a concern to the developing fetus the agency has historically labeled drugs in two different ways, taking into consideration maternal disease, the population of intended use and the frequency and severity of adverse fetal outcome.

If it is felt that the benefits of maternal drug use outweigh the drug's potential risks, then the drug is labeled as category D, pregnancy category D and, by regulation, there must be specific wording that is included in the warning

section of the label.

If it is felt that the benefits of maternal drug use do not outweigh the drug's potential risks, then that drug should not be used in pregnancy and it is contraindicated in pregnancy. The product is labeled as a pregnancy category X and, by regulation, there is some specific wording that must be included in the contraindications section of labeling.

[Slide]

On this slide are just some examples of known human teratogens and highly suspect human teratogens that are contraindicated for use in pregnancy. This is not intended to be an inclusive list. Simply contraindicating the drug alone does not equate with true pregnancy prevention strategies.

[Slide]

Beyond contraindicating the drug in labeling, there are additional pregnancy prevention strategies that can be utilized. This slide has several examples that are informational. They

include the black box warning. Any information in the black box warning must also go into product advertising. There could be wording in the warning sections or in other sections of the labeling. The informed consent documents can be included in labeling and are either advised to be used or included when the physician is writing for this drug, and a medication guide which is required by law to be issued when the drug is dispensed.

[Slide]

There are other pregnancy prevention strategies that are active interventions. These include such things as pregnancy testing and contraceptive use. These typically require the healthcare provider and the patient to actually do something.

[Slide]

The strategy of pregnancy testing addresses that first goal of pregnancy prevention, that no pregnant woman will get the drug. It is useful as a risk management strategy in preventing that only with the first pregnancy test that is

done. Pregnancy testing does not address the second goal, that women do not get pregnant while taking the drug. It allows for early detection of pregnancy and prevention of further exposure to the developing fetus.

But simply stating that a pregnancy test should be done is likely to be insufficient as a pregnancy prevention strategy. Other aspects of pregnancy testing need to be addressed, such as when to start pregnancy testing in relation to beginning the drug and the number of pregnancy tests that should be performed. Also, how pregnancy testing should be continued throughout therapy is important. For example, should the test be done monthly or periodically without any specificity as to what that periodicity would be?

How should pregnancy testing be continued after stopping the drug? It is hoped that this would be driven by the drug's pharmacokinetic properties. Also, the test specifics such as test sensitivity, the types of tests or the setting for testing.

[Slide]

This next strategy of contraception addresses the second goal of pregnancy prevention, that women do not get pregnant while taking drug. Contraception does not address the first goal of no pregnant woman getting the drug. Again, simply stating that contraception should be used is likely to be insufficient as a pregnancy prevention strategy and other aspects of contraception use need to be addressed, such as when to start contraception in relation to beginning therapy; that contraception be used consistently throughout drug therapy; how long to continue contraception after stopping the drug, again a recommendation that would be based on the drug's pharmacokinetic properties; and the specifics of contraception such as the types and the numbers of acceptable methods.

[Slide]

There are numerous other pregnancy prevention strategies that could be used. The strategies that are listed here are not specific to pregnancy prevention and have been used more

generally in other risk management programs. These strategies will actually be discussed in more detail in the next presentation by Dr. Trontell.

[Slide]

It is unlikely that the two goals of pregnancy prevention will be met if the patient and the provider do not understand the risk to the fetus and actively work to mitigate it. Strategies should include that females of childbearing potential are definitely informed of risk to the developing fetus but, in addition to being informed, the woman must understand the risk and she must demonstrate behavior that is commensurate with the understanding of that risk.

[Slide]

Strategies to prevent pregnancy are very complex. The ultimate goal of pregnancy prevention is to prevent fetal exposure to the drug both at drug initiation and with continued use of the drug. It is important to remember that not all teratogens are equal, therefore, pregnancy prevention strategies must be tailored to the specific drug.

This is not a "one size fits all" process.

DR. GROSS: Thank you, Dr. Uhl. The next speaker is Dr. Anne Trontell, who is Deputy Director, Office of Drug Safety at the FDA. She will talk about selecting risk management tools: considerations and experience. After her presentation we will take questions. Thank you.

Selecting Risk Management Tools:
Considerations and Experience

DR. TRONTELL: Good afternoon.

[Slide]

As Dr. Gross told you, I will be describing some considerations and experience that FDA has with selecting risk management tools.

[Slide]

I will start with two definitions of risk management program goals and of risk management program tools. Then I will state some general considerations in selecting tools for risk management. I will then recapitulate some of the concerns that have been expressed today with the current isotretinoin risk management program, and

then suggest some candidate tools that might address those concerns. I will describe two related risk management programs and compare them to the isotretinoin risk management program, and then give you some impressions about the relative advantages and disadvantages of some of the tool options available to us.

[Slide]

In the context of risk management programs, goals are described as the ideal product use scenario or vision statement. We have heard about them many times today. These are tailored to the product-specific risk concerns and, as goals, stated in absolute terms may not be fully achievable. An example of a goal is that no fetal exposure shall occur and the two goals of the isotretinoin program have been articulated several times today.

[Slide]

Again, in the context of risk management programs, tools are defined as those processes or systems that are intended to enhance safe product

use by reducing risk. These tools are chosen considering the severity, reversibility and the frequency of the risk that is attempted to be minimized.

[Slide]

Some general considerations are available in selecting risk management tools. Ideally, each tool should add value in attaining the risk management program goal. In choosing tools, one should seek those tools that have proven effectiveness in reducing risk. One should also seek acceptability by the healthcare system and by patients as well as practitioners, and low burden on the healthcare system. In selecting tools, one should also seek to avoid those that place unnecessary limitations on the beneficial uses of the product. In recognition of the potential confusion and burden, one should also avoid the creation of multiple customized tools that might add to confusion. Insofar as possible, one should seek, in designing tools for risk management, to avoid unintended consequences or paradoxical

worsening of risk in attempts to reduce it.

[Slide]

For purposes of this presentation and discussion, I am going to talk about tools in four broad categories and, quite frankly, spend most of my time talking about those that go outside of the product labeling that Dr. Uhl described so well for you just a few minutes ago. Just to be clear, product labeling, sometimes referred to as the package insert or PI, is largely targeted to healthcare practitioners--physicians and pharmacists mostly.

So, the first category that I would like to describe I will term education and outreach. This involves any of a variety of educational materials that might be given to patients or to practitioners. This might take the form of brochures or videos or patient information such as patient package inserts of medication guides.

The second broad category is one that is difficult to capture in a single term. For want of a better one, I will refer to them as reminder or

prompting systems. These are voluntary systems that make it easier for individuals, be it physicians, pharmacists or patients, to do the right thing and follow the necessary risk reduction efforts. These may take the form of stickers, informed consent or limitations on product supply or unusual product packaging.

The last category that I will describe is limited distribution systems. These restrict the prescribing, dispensing and use of a product to selected groups of physicians, pharmacists or patients, and they are often linked to mandatory compliance with some form of risk management.

[Slide]

In terms of the experience that we have in the agency with tools being applied in risk management, when it comes to product labeling and education outreach, in fact, there is quite a large number of programs. Obviously, all products have package inserts that have been approved by FDA. So, there is extensive use of educational material, however, evaluation of these materials for their

effectiveness has been done in very few instances and some of those evaluations, looking at changes in labeling or at "dear healthcare practitioner" letters have shown somewhat disappointing results in terms of their ability to affect behavior.

With respect to the reminder or prompting systems, these have been used relatively infrequently so we have relatively few models upon which to base our experience. Effectiveness of these has largely been untested and, in fact, the evaluation today of the isotretinoin risk management program represents an important step forward in evaluating such systems.

The last category of tools, those involving limitations and distribution, are used most uncommonly, downright rarely. These typically are used for small patient populations that have limited therapeutic options. In these programs the logistics of setting up the limited distribution system involve some form of registration of the participants and that registration, in fact, enables daily collection that has allowed us to

evaluate their effectiveness and those have been demonstrated effective at this point. I will elaborate further shortly.

[Slide]

Again, to cement these categories for the discussion to come, some examples of drug products in the reminder or prompting system would include isotretinoin, the closely related program that is in place for alosetron and yet another one to give you as an example is the drug product lindane, where in the past year restrictions have been made on the amount of that product that can be dispensed to patients to minimize the likelihood of over-use that has led to toxicity.

With limited distribution we have approximately six programs listed here, bosentan, clozapine, dofetilide, mifepristone, thalidomide and xyrem. Those that have the asterisk by them are ones where laboratory testing is required as part of these programs.

[Slide]

Let me now turn to some of the concerns

that have been expressed today with the performance of the current isotretinoin risk management program. As Dr. Pitts indicated, refills are not supposed to occur. They have been reduced in the current program but still occur at a rate of approximately 2.5 percent of all the prescriptions. We have evidence from the pharmacy compliance survey and from patient reports that some prescriptions, a relatively small amount, are being filled without the stickers being present. Perhaps more concerning is the self-reported data from patients suggesting that stickers may be being used without concordant pregnancy testing, estimated at 9 percent from our analysis of the Degge survey.

[Slide]

The other important issue however that we really want to address is those issues of pregnancy exposures that have occurred. We have in our analysis at FDA estimated that the number of patients initiating therapy while pregnant is approximately 6 percent. We have heard other estimates from the sponsors today that it may be 13

percent or perhaps as much as 25 percent. In some instances this represents inadequate pregnancy testing, perhaps two tests not being done, and correct timing and other forms of errors.

There are other pregnancy exposures that have been reported to us voluntarily, and the majority of those are those that have occurred during isotretinoin therapy or in the month following. The reports that come to us have suggested these largely reflect problems either in poor or absent contraception by patients. In some instances the case reports have described individuals who plan to be abstinent but had unanticipated sexual activity and were unprepared with contraception.

In addition to these concerns, one that has not been emphasized to any great extent today but which, through case reports, have been made known to us is that this product is used in some unknown percentage by individuals without the benefit of medical supervision. There are individuals, some described in the MMWR article

described previously, who have obtained the product illicitly through the Internet. They may have borrowed it from a friend or, in some instances, may have made use of leftover pills from a prior course of therapy.

[Slide]

An additional concern, not about performance of the system, gets at the issue of evaluating the performance of the program. We are limited in our ability to estimate the extent of pregnancy exposures. We are relying in our presentations today on voluntary reports and on voluntary patient surveys. As has been suggested, the existence of multiple surveys actually permits the possibility that a patient's information may be counted more than once. Also, in estimating the extent of isotretinoin exposure it is important to know that these are estimates and based upon pharmacy data, and don't let us know the true extent or duration of isotretinoin exposure among females of childbearing potential.

[Slide]

Let me now turn to some of the tool options that we might consider to address each of the concerns that I have just described. Looking at sticker use and appropriate prescribing or dispensing of the product with stickers, one might look to the broad category of education and outreach for opportunities for improvement. There might be better education of pharmacists and physicians to improve what we believe are good faith efforts to prescribe and dispense this product appropriately.

If we are to think of the next category of potential tools, one might think of ways that we could increase the number or types of reminder systems to make it more difficult for individuals to forget to do what is appropriate. In this arena we have limited models to draw on for drug exposure and, as our colleague from Kaiser described, it may be that some of the disease management models that exist for chronic conditions may be helpful to us.

In the last category, where limitations might be imposed upon prescribing or dispensing by

healthcare practitioners, one might imagine broadly various scenarios where training, certification or registration might be required of practitioners and that that might also make some requirements for systems to be in place that obligate compliance with key program elements and would actually allow us better monitoring of program performance.

[Slide]

Turning to concerns about the extent and completeness of pregnancy testing, two options in this area are very similar to what I have just described. We might try more effective education for healthcare practitioners. Similarly, we might have other mechanisms to try and do a job of reminding them in a better fashion. Similarly, limitations may be imposed so that only those individuals, through some process, who have been documented to do a good job of pregnancy testing would be allowed to prescribe this product. Again, looking to the experience in the Kaiser program, there may be some opportunity to consider whether documentation of pregnancy test results may, in

fact, be one mechanism to improve compliance with this form of pregnancy prevention.

[Slide]

Turning to contraception, I think it is important that we acknowledge the great difficulties in intervening in what is a complex and private human behavior. It is clearly very sensitive for both patients and physicians to discuss this. It is certainly a great challenge in the instance of adolescents who may be receiving drug therapy with their parents present, but I would submit for patients of all ages the assumptions and misinformation that might occur around the sensitivities and awkwardness lead to some errors in factual information.

The other important challenging factor around intervention and contraception is that behaviors of individuals are, not just contraceptive behaviors, are influenced by knowledge but they are not controlled by knowledge in that they are complex attitudinal and behavioral components that should be addressed.

[Slide]

Around contraception, however, let's go back to sort of our three-stage model of intervention of tools. If we look to improving education and outreach to patients we might increase their knowledge about the need for two simultaneous effective methods of contraception and perhaps we may need to address issues of what are ineffective methods of contraception, particularly in light of the comments from our colleague from OTIS. Also, I might add to this slide that we may also need to reinforce the importance of continued contraception after terminating therapy.

[Slide]

If we were to look to the reminder or prompts category of tools, we might look to some form of counseling though that may take any of a variety of forms. We might hope that counseling would allow some reinforcement of knowledge of appropriate contraceptive behaviors and could address attitudes that might influence appropriate contraceptive use, issues about planned or

unplanned sexual activity and other sensitive issues that may deal with partner compliance, cooperation or resistance to the use of contraception.

These reminder systems could be put in place on a one-time basis. We might suggest periodic reinforcement would be a preferred strategy but we invite your commentary. As you may be aware, there are a number of methods that can be put in place involving counselors or some technologies that are now available, and were described earlier, such as interactive voice recognition software, moderated chat rooms and so forth.

[Slide]

Turning to the third category of tools that we might use to address contraception, we are again getting to a difficult and sensitive area but one might imagine ways that we might try to limit patient access to drug to those who have demonstrated the appropriate knowledge and skills and behaviors around the use of contraception. I

will suggest this could happen perhaps through some form of counselor certification that would attest to the patient's level of commitment and demonstrated skills in their ability to use the chosen contraception. Again, some periodic contact via counselors or some IVR technology might allow screening for high risk behaviors and the opportunity to intervene to direct those people to lower risk strategies or to temporarily suspend their exposure to the drug. I think it is highly extreme, but for purposes of discussion, there are models in the case of tuberculosis testing with directly observed therapy. Obviously, in the area of contraception this is challenging. You might look to use of oral contraceptives or contraceptive patches, pill counts or other methods that you might track adherence with contraception.

[Slide]

In talking about tools, however, we need to address the issue that contraceptive failures occur, and I use this term broadly to include failures of the method as well as failures in

practice. One option to be considered is if some level of contraceptive failure is acknowledged to occur is that we may want to explicitly limit exposure of females of childbearing potential to this product, and to do so perhaps based on the severity of the acne that those individuals experience. Again, the possible mechanisms that this could be done are through some form of required documentation of acne severity, a prior authorization mechanism, second opinion or some other check mechanism, again, to assure that females of childbearing potential who are exposed to isotretinoin are only those who have the most severe forms of acne that we saw this morning.

[Slide]

Talking about medically unsupervised use really taxes our imagination because we are talking about people who, by definition, are going outside the system where we have the most influence. But, again, we might hope, back to our education model, that we could educate individuals better about the risks of using these products without medical

supervision, and perhaps there may be some innovative mechanisms around product packaging where we could make note of the risks of unsupervised use, obtaining it through the Internet or sharing it with other individuals. One other possibility might be to, in fact, limit the amount that is supplied to the patient to some amount less than the typical 30-day supply that is currently dispensed to decrease the opportunity for people hoarding or sharing with other individuals. Obviously, the manufacturers of isotretinoin share with FDA a great desire to constrain illicit Internet sales.

[Slide]

Let me now describe two risk management programs briefly that have been alluded today that may be relevant for comparison to the isotretinoin program. The first one is clozapine, an appealing comparison because it has significant safety risks and it has a risk management program that is administered by multiple manufacturers. There are inter-related data systems that are in place for

this product and the systems have allowed some evaluation of the program's effectiveness. In fact, that information has been used to relax program requirements over the lifetime of this risk management program.

Thalidomide is the other product which has an extensive and effective risk management program also for teratogenicity. It is important to note that this program, although very appealing in terms of its experience, has had very limited use among females of childbearing potential. Only about 5 percent of the total population exposed to this product have been women of childbearing potential, only about 4,000 individuals.

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Clozapine, briefly for those who may not be familiar, is an antipsychotic that carries the risk of agranulocytosis, and this risk is managed by a program of weekly to biweekly blood testing to assure that the white count is adequate. The pharmacist is required to view the white count documentation. The white count must be presented

in order to dispense the product, and only registered pharmacists, patients and physicians are able to access this drug product; not every pharmacy is able to fill these prescriptions.

[Slide]

For clozapine there is a centralized registry of patients. This is reserved for those patients who are not to be rechallenged with this drug based upon their prior experience of having had a lowered white count while taking it. In addition to the centralized "do not rechallenge" registry, there are independent sponsor programs that permit the weekly and biweekly testing to be done. This program does not have any patient survey or education, considering that the population receiving it is largely individuals with refractory schizophrenia, but there is extensive education for the providers, both the physicians and pharmacists, about what they are to do in administering the program.

[Slide]

For thalidomide the goal is that no fetal

exposure should occur because of its teratogenicity and, like clozapine, only registered patients, pharmacists and physicians are able to access this drug. Pregnancy testing is done on female patients according to their pregnancy risk category and that is based upon their age and fertility status. Physicians report to a centralized database the negative pregnancy status of their patients in order to authorize that prescription being released.

[Slide]

Patients must also report via IVR on their risk factors for pregnancy exposure. Those individuals who give responses suggestive of high risk behaviors are routed directly to a live operator of action and potential intervention.

Pharmacists, at the time of dispensing this product, check the central database and look to see if the information from the physician and the patient are both appropriate and permissive for them to dispense the product. The system allows through its central database the ability to track

pregnancy exposures, at least those that are not lost to follow-up. Much like isotretinoin, there is an extensive educational program associated with this product. There is a medication guide, informed consent, a video and many other materials.

[Slide]

Let me now make some comparison of the three programs, isotretinoin, thalidomide and clozapine. I have abbreviate each here by their first letter.

Warnings exist in physician labeling or package inserts for all of these products. Patient education materials, medication guides and patient informed consent are extensive both for isotretinoin and for thalidomide.

[Slide]

All programs do require laboratory testing but there are some subtle differences that I will describe. In the case of clozapine, actual documentation of test results is required in order to receive the product. For thalidomide the form of laboratory testing can come via the physician

report of the test being positive or negative. In the case of isotretinoin, a physician uses a sticker to attest that pregnancy testing has been done and that those test results are negative.

[Slide]

With patient registration, this is done for all patients, both male and female for thalidomide. In the case of clozapine, a central registry is maintained only for those patients who are not to be rechallenged with the drug product. There is no registry for patients taking isotretinoin.

Physician registration is required for prescribing for both thalidomide and for clozapine. For the case of isotretinoin, physicians enroll in the program. There is mandatory enrollment to get stickers, but physicians are technically allowed to prescribe this product without stickers.

[Slide]

Pharmacy registration is required to dispense both thalidomide and clozapine but not for isotretinoin.

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When it comes to tracking program performance, patient behaviors are captured through the IVR component of the thalidomide system, and for the isotretinoin program it is captured for the proportion of patients that respond to the voluntary patient survey. Patient exposures are captured for all patients taking thalidomide and clozapine is captured uniquely only for those patients who are not to be rechallenged with the drug. There is direct tracking of outcomes by the thalidomide and clozapine program, thalidomide of pregnancy test results and clozapine of white counts. For isotretinoin there is voluntary reporting, either directly to the agency or through the survey, of patient behaviors.

[Slide]

Let me now discuss some of the advantages and disadvantages we might think of broadly when we are thinking of the various categories of tools that I have described. If we were to consider increasing education or outreach for isotretinoin,

we could see as advantages that this is an option that is likely to be acceptable to most of the participants in this therapeutic relationship. It is feasible. It would involve no change in product access and might allow time for the current program to see if experience changes or improves.

Disadvantages in the area of education and outreach are that education and outreach alone have not yet shown a good track record of effectiveness, and it may be particularly challenging to think of changing contraceptive behaviors simply by adding education and outreach.

[Slide]

If we were to turn to reminder and prompting systems as a way to try and fortify the response in the isotretinoin risk management program, advantages of such an approach might include the continued autonomy of physicians, pharmacists and patients. There is no mandatory component. By definition, these are guiding little nudges to make sure you are supposed to do what is right. There might be an opportunity with these

reminder systems to allow ongoing education and reminders about the risks of the product and how to use it most safely. In comparison to the next category of tools I will describe, limited distribution is certainly much less intrusive.

Disadvantages in this category, as I have stated previously, are that for drug therapies we have limited experience and limited models to borrow from. The effectiveness of these are unknown, and you have seen the experience with the current program outlined for you today. As has been mentioned by some individuals already, we need to consider the time and financial burdens that might be entailed with counseling or some form of disease management around this issue.

[Slide]

Turning now to the last category of limitations imposed on the prescribing, dispensing or use of this product, potential advantages in designing a program around such a system would be that we could theoretically limit access of the product to those individuals who would adhere to

the critical risk minimization tools--counseling, pregnancy testing, and so forth.

Again, the nature of limiting distribution requires that you have to have some list of who can and can't give the product and that listing, in fact, gives you the ability to register individuals and have better data to evaluate the program in terms of its baseline performance or changes over time.

An additional advantage, whether it be done explicitly or implicitly, is that the burdens and logistics of such programs are likely to limit the exposure of females of childbearing potential, if only for the perceived tassel of complying with the limited distribution program.

In terms of disadvantages for isotretinoin in comparison to at least the limited distribution program that we have as a model for thalidomide, the effectiveness of the S.T.E.P.S. program in young, fertile women is not yet documented. Again, we would consider that restricted or limited distribution programs would impose time and

financial burdens upon the healthcare system and would probably introduce a real possibility of limiting access to the drug to those people who might legitimately benefit from its use. It is also important to recognize that the creation of substantial barriers around product access may increase the incentive for individuals to go outside of the system, obtain the product illicitly and, in that way, bypass any access to some of the safety measures that we are trying to promote.

[Slide]

Let me conclude by reminding you of the general considerations I used at the beginning of my talk. If we are to consider modifying or selecting new risk management program tools for isotretinoin we want to keep these considerations in mind. First, that we seek evidence for effectiveness of any tools and the high likelihood that tools added would add value to the attainment of the risk management program goals; that drawing upon effectiveness, familiarity and acceptability, we would like to try and stay as close as possible

to familiar tools that are already being applied in practice.

Where possible, we should avoid unnecessary limitations on product use, and we should anticipate that any of our interventions are likely to impose time, cost and access burdens by constraining access to the product, and we should be wary of the possibility of unintended consequences of our very good intentions. Thank you.

Question to the Speakers from Committee

DR. GROSS: Thank you very much, Anne. That was extremely helpful. The floor is now open for questions from the committee members for these two speakers. Dr. Gardner?

DR. GARDNER: Dr. Trontell, I don't think it really came home to me until I heard your words literally saying that the registration of physicians for isotretinoin is voluntary and that physicians do it to get yellow stickers but technically they can prescribe without yellow stickers. So, that triggers two thoughts in my

mind. One is that, therefore, the burden of overseeing this effective stopping is really at the pharmacy when prescriptions come through without stickers, in the first instance.

Then, second, it calls into question for me all of the information we have had today about how mail order prescribing doesn't happen, or is not allowed, or is unauthorized. Suddenly I am very confused about how much might be going on.

DR. TRONTELL: The use of the term voluntary I think is in the strictest sense. I think we have seen from the data presented today that use of the stickers is high, and I think the experience would suggest that individuals are largely trying to do the appropriate thing. Technically, pharmacy law administered at the state level allows a pharmacist to honor any prescription, and if a physician wanted to make a case that they could prescribe this product without a sticker it might be that a pharmacist would permit it to be so.

I think there is the implication in the

program, because of the risk management program that is spelled out so explicitly in labeling, that individuals would comply; that individuals who didn't comply might, in fact, face certain risk, if only from a liability standpoint. So, it is largely through influence that this program has its extensive use, at least as we have seen it described today. I am not sure if that answers your question sufficiently.

DR. GARDNER: Yes, I think so. The grey area for me still falls into the mail order department.

DR. TRONTELL: In the area of mail order, we were told that there is no known exposure. In the data that were presented today, some of the data streams include prescriptions that might come from mail order but we did not do an explicit breakout of that. That is certainly something that could be done though but probably we would be unlikely to give you an answer before the end of this meeting tomorrow.

DR. GROSS: Dr. Schmidt?

DR. SCHMIDT: Helen Keller was interviewed by a newspaper reporter one time and was asked what could be worse than losing your sight, and she said losing your vision. Certainly, I think your talk brings us to a vision. One of my visions, and I just reflect on this, is that one of the things we could also do is find better retinoids and retinoids that don't have teratogenicity. In Maybock's book on dermatotoxicology there is a chapter where he talks about the class of retinoids called n-phenyl retinamide that appear to bear no teratogenic effect risk although they have a good effectiveness. So, hopefully, in the future we will be able to also solve this problem by finding retinoids that do not have this kind of risk.

DR. GROSS: Dr. Bergfeld?

DR. BERGFELD: I would like to revisit the pharmacy. We have heard a lot of things evolve around the pharmacist and in our information sent to us we also have been made aware that many major pharmacies have dropped out of this program. There was no explanation but I would assume it was

because it is so time intensive. If the pharmacist will still continue, no matter who does it, to be the police in any program that is evolved, I think that we should hear from the pharmacists and the reality if they are taking on that responsibility.

DR. TRONTELL: If I may answer that with a clarification, the dropout problem that was described in the review from the Office of Drug Safety was dropout from pharmacies participating in the compliance survey. That wasn't meant to imply that those pharmacies weren't, in fact, complying with the sticker program. They declined to do a separate survey of their prescriptions to see, in fact, at what level of compliance they were performing. So, there is a difference between consenting to be measured and consenting to participate in the program. We have no evidence to suggest that any particular pharmacy chain has elected not to use the sticker program.

DR. GROSS: Anne, I would like to ask you why you would have confidence in more education. It hasn't seemed to work so far and many of the

quality improvement studies done on education show that it is of limited benefit.

DR. TRONTELL: I think, personally, education is necessary but not sufficient to change behaviors. I suspect in the arena of contraceptive behavior--but this is largely based on my clinical experience as a pediatrician and dealing with the vast challenge of teenage sexuality--that there is a lot of misinformation and, in fact, it may be perhaps even more challenging for young adults in an office visit for a physician to presume that a patient is less than well informed about what are effective methods of contraception.

But I do agree. We have seen a quite thorough educational program put in place with the current isotretinoin risk management program and I am not entirely clear what would be the best mechanisms to improve that. We might ask some individuals who are particularly well informed about education and information of individuals.

DR. GROSS: Dr. Katz?

DR. KATZ: Dr. Trontell, you in part

clarified Dr. Gardner's question, but I want to emphasize that the term voluntary would signify to non-dermatologists that, "oh, that is just up to the doctor to do it." In real life you don't get a prescription filled without those yellow stickers. Whether the patient, on the questionnaire, remembers it or not, basically, at least around here, if it goes to the pharmacist without a sticker it doesn't get filled.

DR. TRONTELL: It is important to note that to my knowledge of the pharmacy compliance surveys that have been done, those are for the prescriptions that have been filled so there, in fact, is an imperfect way of capturing the prescriptions that have been refused by the pharmacy.

DR. BIGBY: This is a simple question for anybody who can answer it. Why did CVS and the large chains drop out from the pharmacy compliance survey?

DR. KIBBE: Money. In most cases large chains are very tight with how they expend

resources and, unless they are compensated for doing extra paperwork, they don't want to, and if they are not mandated to do it or not compensated for it, they would opt out of it. There was no contingency that meant that they would then lose the business of filling prescriptions because they didn't do the survey and I don't think there was a benefit to them.

DR. BIGBY: So, they were not paid to do the survey?

DR. ACKERMANN SCHIFF: Susan Ackermann Schiff, Hoffmann-La Roche. Yes, they were compensated per prescription they audited to participate in the survey, although the compensation was minimal.

DR. GROSS: Dr. Ringel?

DR. RINGEL: I have two comments, one is normal and one is bizarre. The normal one is that I do think education is helpful. I think it is also helpful for the physician and for the patient. We are given a list of regulations. That doesn't mean that we understand why those regulations are

in place. For example, it used to be that isotretinoin was taken on the second or third day of the menstrual period and then all of a sudden it changed so that now the pregnancy test is done during the menstrual period and the drug is started within seven days. Now, why was that change made? No one ever explained it to me and I remember sitting down with this and saying I don't get it. I kind of thought it through and now it makes sense to me but it wasn't intuitively obvious. I get the impression that that is something that folks are messing up a lot, the seven-day period and, you know, why should we do the pregnancy test then.

Another thing is why two pregnancy tests? I mean, if the first one is positive the second one is going to be positive so why bother to do the first one? I mean, somebody could argue that. I think people should have like a chart so this is the regulation and this is why. I think it would be helpful for both physicians and for patients.

The bizarre one is this, I have an idea for a reminder or a prompting system. If everyone

were on a primary form of contraception and did it right and complied all the time we would have a very low pregnancy rate. You can document that people have had a vasectomy or tubal ligation or are getting monthly Depo Provera shots or have an IUD, but you can't monitor people's use of oral contraceptions. I think somebody might need to tell me if the technology for this is there; I think it is. This would have to be an electronic solution. Let's have an electronic pill box and it has 28 days, and you put one pill in each day. There is a little microcomputer thing and each time you open up the little cell and take one the date is marked on this little computer card, kind of like the thing you have in your digital camera. At the end of the month you take that to the pharmacist and he puts it in a card reader and if you have taken your pill every day he will give you your next Accutane. Wait, I am not done.

[Laughter]

Now, if you don't take your pill though there is this little buzzer that goes off and this

little annoying ding, you know, the ding-ding-ding to drive you crazy and remind you to take it. Then--then, one more thing, if you don't do it two days in a row there is a red light that goes on and underneath the red light it says "stop isotretinoin; use alternative birth control; call physician immediately." If you have missed two days in a row and the red light goes on and that is it, and then you would know if people are taking it.

DR. GROSS: And then what do you do when they put the pill in the wastebasket?

DR. RINGEL: Well, you have to assume that nobody is trying to get pregnant on Accutane; nobody says, "oh gosh, I really want to have a baby with a birth defect." I don't think people are going to do that, I really don't.

DR. GROSS: Sarah Sellers?

DR. SELLERS: Dr. Trontell addressed the comparison of risk management programs including clozapine. I think it is important to point out that under this program they require registration

of pharmacists and not pharmacies. In the presentations I have seen concerning the effectiveness of other risk management programs, specifically thalidomide, they have noted that the system does break down at the level of the pharmacy because if a pharmacy is registered and, for instance, that pharmacy is open 24 hours a day there may be pharmacists during the day that are very well trained in the program but then a shift pharmacist comes in for the midnight shift who is not well trained. So, this is where they were seeing breakdown of the program. Registering pharmacists, on the other hand, would eliminate that risk.

DR. GROSS: Dr. Whitmore?

DR. WHITMORE: Dr. Gross, you had brought up a couple of different times education and also why people wouldn't use two forms of contraception. Mr. Sisto from one of the generic companies had shown us data on pregnancy rates and, just to be complete in his reporting of the pregnancy rates, he actually gave us rates after persons had

completed Accutane. So, even in women who were 30 days from Accutane when no effect of the drug should be seen at that time what he showed in that data was that one in three of those women who became pregnant 30 days after the drug had abortions.

So, that just brings up the obvious, that women have abortions outside Accutane, and I don't know what the rate of abortion is with pregnancy in this country but I wonder if it is any different with Accutane versus with women who get pregnant who are not on Accutane. It just brings up the obvious, that for some women abortion is okay and for others it is not. For those for whom it is okay, I think that they take the idea of two forms of contraception more seriously than others. There were women who did get pregnant when they were on Accutane who did not have abortions so, obviously, there are women who will not have abortions even for medical reasons.

In summary, if we want to control this outside of what women want, the only way for us to

do that is to insist that they have some form of adequate contraception such as Depo Provera. That is the only way we are going to get 100 percent--well, I don't know if it is 100 percent but that is the only way we are ever going to get close to 100 percent prevention of pregnancy when somebody is on this drug. You know, this is independent of whether abortion is okay or not okay. If we really want people not to get pregnant while on this drug, we are going to have to insist that we enforce that in some way.

DR. GROSS: Yes, I think we may have an answer.

DR. MITCHELL: Well, it is a partial answer. If I have the privilege tomorrow I could actually present the data themselves. But we track the rates of pregnancy and the rates of elective abortion not only during Accutane therapy and the month following but in the five months following that. I would be happy to present it tomorrow. I think it is sort of an internal data set that bears on the question you asked.

DR. GROSS: Yes, and my comments on education were two-fold. One is that education already takes place in this program and seems to fail. The types of education that traditionally fail are passive education. Those that are interactive where the person who is being educated somehow participates in the session, those studies indicate that that type of interactive education is much more successful.

MR. HUBER: I am sorry, I think we may have the answer to the previous question if I understood the question correctly.

DR. GROSS: Go ahead.

MR. HUBER: I think we have the data. Could you repeat your question, please?

DR. WHITMORE: Well, my point was that women in this country have abortions and there are probably women who are on Accutane who think I can have an abortion if I get pregnant and a woman, independent of being on Accutane or not, had she got pregnant would have had an abortion. And, the only way we are going to control this and say 100

percent we do not people getting pregnant while on this drug is to insist that there is a mechanism by which they can't get pregnant, and that would be something like Depo Provera but, again, that is not 100 percent but at least we are eliminating the behavioral failures of birth control pills and things like that.

MR. HUBER: If your question was the rate of abortion in the population in general, we do have that data if you would like to see that.

DR. WHITMORE: Surely.

MR. HUBER: Could I have the slide on, please?

[Slide]

The data source is Henshaw Family Planning Perspective, 1998. If you look at this, there is the age, age at outcome and what these are is estimated rates of unintended pregnancies, unintended births and abortions per 1,000 women, age and marital status and percentage of unintended pregnancies ended by abortion. If you look, we have unintended pregnancy, unintended birth,

abortion and percent ended by abortion. The numerator is the women who are in the group. The denominator is the age range. As you can see from these data, abortion and percentage of unintended pregnancies ended by abortion is quite high.

DR. GROSS: Dr. Honein?

DR. HONEIN: I had a question about how the registration works with the thalidomide program in respect to whether that is similar or not to what is being proposed for isotretinoin. Is there a unique patient ID number? If so, does the registry also capture the patient's name that is linked to that ID number? Or, how do you eliminate duplicates if you are using a unique ID number if there isn't a name linked with that somehow?

DR. TRONTELL: Some of the details we may not, in fact, have for you. Bear in mind, however, that thalidomide is in a single source environment so that potential duplication is not an issue for that product. The issue of how the patient is explicitly registered in the system, whether that involves an identifier--

DR. HONEIN: Even in a single source environment you could have duplication over time if someone had multiple prescriptions but not continuous, or no longer had their patient ID number.

DR. UHL: We can get that answer for you.

DR. TRONTELL: Right. Bear in mind too that thalidomide's use is largely for the use of oncology indications. These are people who are very ill, who typically are not on the product for very long and are receiving it in a way that--you know, some of that in and out therapy that we know happens with isotretinoin isn't perhaps likely to occur. We will seek that answer for you.

DR. GROSS: Dr. Raimer?

DR. RAIMER: Dr. Trontell, I was just wondering, and you may have partially answered the question, with the S.T.E.P.S. thalidomide program I know the numbers of women on that drug are very low but what is the incidence of pregnancy with the S.T.E.P.S. program and thalidomide?

DR. TRONTELL: Dr. Uhl will answer.

DR. UHL: We actually have some backup slides on this as well.

[Slide]

This is some information that we have on the S.T.E.P.S. program for prescribing of thalidomide. Thalidomide was approved before September of 1998 but it was ready for marketing and implemented in September of 1998. So, from September of 1998 until April of 2003 there were approximately 400,000 prescriptions in totality written for thalidomide. There are approximately 80,000 patients that were exposed to thalidomide and the majority of the use was for patients with oncologic indications.

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Here are the demographics of patients that have taken thalidomide. As I said, there were 80,000 patients. More than half of those patients were male patients and less than half were females. Less than 5 percent, in the ballpark of about 4,000 patients were females of childbearing potential. The demographics of users of thalidomide are

considerably different than the demographics of patients that use isotretinoin. The mean age was 66 years and the range was anywhere from less than one year to over 100 years. For females of childbearing potential the mean age was 42, with a range of 13-59. The mean length of therapy was four months for thalidomide.

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In that time period there was one pregnancy that has occurred in the S.T.E.P.S. program and here is some specific information about that case. This woman was a 44 year-old gravida 5, para 3 with history of 2 previous spontaneous abortions or miscarriages that were unrelated to thalidomide therapy. This patient had high risk malignant melanoma.

What is pertinent about this patient's case is that she was intolerant of oral contraception therapy and used two methods of barrier contraception, condom and spermicidal foam. In the S.T.E.P.S. program the patient has to have two negative pregnancy tests before they are given

thalidomide and the second negative pregnancy test needs to be done within 24 hours of getting that drug. So, this patient had a negative pregnancy test on the day prior to starting thalidomide. The S.T.E.P.S. program also has weekly pregnancy tests for the first month and subsequent weekly pregnancy tests for this patient were negative on three consecutive weeks. On week four she had a positive pregnancy test and then had a positive quantitative test, and then she went on to have a spontaneous miscarriage on day 63 of her menstrual cycle.

DR. GROSS: Robyn Shapiro?

DR. SHAPIRO: That actually was half of my question. Risk management is, of course, weighing and balancing benefits and burdens of what you may decide to do so I guess, Dr. Trontell, I am wondering if you could speak, while it is much less analogous, to clozapine and the etiology of that more restrictive risk management program? What were the numbers of bad things happening there that convinced you and the agency--you and the sponsor, whoever it was--to go to the next level in terms of

restrictiveness of a risk management program?

DR. TRONTELL: The clozapine program was put in place at the first marketing of this product. I don't have first-hand knowledge so I am going to be reporting information that is second-hand. I will invite any who may wish to correct me, but in the clinical trial experience of this drug there was a significant and concerning rate of agranulocytosis. I recall it as being on the order of three percent of so. Please don't quote me on that.

So, the concern with this product, which did show benefits for a particularly difficult population to treat, was how that might be prevented. So, from the start, at the time of approval, the system was put into place. I am told that advocates for individuals with this illness actually advocated for the collection and registration of patients. My understanding is that the experience of agranulocytosis in the program in practice actually is less than the percentage that was observed in clinical trials. The white cell

testing doesn't prevent the occurrence of agranulocytosis. Presumably you see a reduction in the white cell count before it becomes critically low and it may be, in fact, that individuals are operating cautiously when they see a downward trend and they operate proactively to remove the patient from the drug product. So, that was instituted from the beginning.

Similarly, it is important to note that the thalidomide program was also instituted at the time of approval. Once a drug product is on the market it is a little more challenging to redesign the methods in which individuals have become accustomed to using it.

I will make one additional comment. There is also probably a difference between going to a pharmacist and showing them a white cell count, which is really nothing that you individually influence, and going to a pharmacist and handing them a pregnancy test result.

DR. GROSS: Dr. Crawford?

DR. CRAWFORD: This question is for either

Dr. Uhl or Dr. Trontell. In looking at the goal of no fetal exposures to isotretinoin for the at-risk population as females of childbearing potential, in some of the presentations this morning there were suggestions that risk management programs also include men. This would be a new category of risk, not the at-risk population, knowing that people may share drugs. Though, given what was said about looking at undue burden, I would like to ask the representatives of the FDA to please comment on that.

DR. TRONTELL: With thalidomide there is actually some potential concern for risks relating to paternal use of the drug and potential levels of the drug product in seminal fluid that may or may not present actually a risk to the female partner of those individuals. So, in fact, pregnancy prevention is directed to those individuals. They are advised to use barrier methods of contraception.

With isotretinoin some of the concerns that have extended the program to males gets at the

issue of having a parallel system for males that is different than for females. In fact, a pharmacist who is in a busy practice may have greater opportunity to make an inadvertent error on a female's prescription if, you know, they don't attend to the name or the check box on the sticker, and so forth.

In terms of the issue of sharing drugs, I don't know any evidence to suggest that individuals in intimate relationships are more likely to share products than others but it clearly is something that happens among female patients who are trying to improve their skin sometimes for a specific event. I have heard of swap meets occurring. I think that was described in the MMWR article.

DR. GROSS: Dr. Whitmore?

DR. WHITMORE: In the Accutane Roche briefing package they have information on pregnancies. Among 183 pregnancies, 32 percent occurred in the 30 days after the Accutane dosing. Is there any proposal to address that because that is when they are lost to the sticker system and

other things like that? After the completion of Accutane there is no longer a requirement to qualify in any way to get more drug and that 30-day time period is a period in which we don't want them becoming pregnant.

DR. GROSS: Would anyone from Roche like to answer?

MR. HUBER: There is no specific element aimed at that post population. We have been struggling with how we would catch them in a follow-up cycle. The problem is we can put in the educational components but because they don't have to do anything because they are not requesting more drug, there is not the same incentive as you can have in the regular follow-up. So, our current approach would be to probably put some type of follow-up in the intervention but this is something that if the committee has some guidance on, we would be very appreciative to hear your thoughts on that.

DR. GROSS: I would like to close for the day. I would like to thank the speakers and thank

the committee members for their attentiveness and perceptive questions.

There are a couple of items of business. The committee members can leave all their paperwork here. It will be safe overnight. The committee members do have some homework. Attached to the agenda, behind the agenda sheet for tomorrow, are the questions that we will be considering tomorrow. They will be presented in detail by Dr. Seligman and then we will discuss them and give our opinions and recommendations.

For the committee members, you are all invited to dinner. A bus will be out front at 6:00 p.m. to take us back and forth to the restaurant. So, thank you all. I look forward to seeing you tomorrow.

[Whereupon, at 4:45 p.m., the proceedings were recessed, to resume at 8:00 a.m., Friday, February 27, 2004.]

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