AT DEPARTMENT OF HEALTH AND HUMAN SERVICES

STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE (DODAC)

IN JOINT SESSION WITH THE

DRUG SAFETY AND RISK MANAGEMENT

ADVISORY COMMITTEE (DSARM)

The Dermatologic and Ophthalmic Drugs and the Drug Safety and Risk Management Advisory Committees will meet in joint session to be briefed on iPLEDGE, the risk-management program for isotretinoin products

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order

DR. BIGBY: Good morning. I am Michael Bigby. This is a joint meeting of the Dermatologic and Ophthalmic Drugs and Drug Safety and Risk Management Advisory Committee. We are here to be briefed on the first year of the iPLEDGE Program.

One brief starting announcement and that is that Congressman Stupak will not present in the Open Session this afternoon. He has a written statement that you should all have in front of you.

Introduction of the Commissions

DR. BIGBY: The first thing we need to do is have an introduction of the members of the Committee. Please state who you are and to which organization you belong. I think we would start over to the far right here.

DR. GROSS: I am Dr. Peter Gross. I am Chief Medical Officer, Senior Vice President at Hackensack University Medical Center in New Jersey.

DR. CRAWFORD: Good morning. My name is Stephanie Crawford from the Department of Pharmacy

Administration at the College of Pharmacy, University of Illinois at Chicago.

DR. KING: I am Lloyd King from Vanderbilt University, Dermatology.

DR. PLATT: Hello. I am Richard Platt. I am Professor and Chair of the Department of Ambulatory Care and Prevention at Harvard Mediator School at Harvard Pilgrim Healthcare.

DR. DRAKE: Hello. I'm Lynn Drake from the Department of Dermatology at Harvard Medical School based at Massachusetts General Hospital.

DR. KRAMER: Hello. I'm Judith Kramer. I am Associate Professor of Medicine at Duke University.

MS. GRIFFITH: Good morning. I am Gail Griffith. I am a writer and communications professional. I have served as the Patient Representative to the Psychopharm Committee on Antidepressant Medication for Adolescents and I am recently named the Consumer Rep to the Psychopharm Committee.

MR. KRESEL: Good morning. I'm Peter

Kresel. I am the Industry Representative to the meeting. I am a consultant in regulatory affairs to the pharmaceutical industry.

DR. THIERS: Good morning. I am Bruce Thiers, Chairman of Dermatology at the Medical University of South Carolina in Charleston.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I am an epidemiologist at the University of Pennsylvania School of Medicine.

DR. LESAR: Timothy Lesar, Director of Pharmacy, Albany Medical Center, Albany, New York.

LCDR MOSADDEGH: My name is Sohail Mosaddegh. I am the designated federal official for Derm and Ophthalmic Drug Advisory Committee.

DR. BIGBY: I am Michael Bigby. I am at Harvard Medical School and Beth Israel Deaconess Medical Center and the Chair of DODAC.

DR. SAWADA: Good morning. I am Kathleen Sawada. I am private practice in Lakewood Colorado.

DR. SKINNER: I am Bob Skinner, dermatology, University of Tennessee Health Science

Center, Memphis, Tennessee.

DR. NELSON: Lewis Nelson. I am an Associate Professor of Emergency Medicine and a medical toxicologist in New York University School of Medicine.

DR. MITCHELL: Allen Mitchell, Director of the Slone Epidemiology Center at Boston University.

DR. DAY: Ruth Day, Director of the Medical Cognition Laboratory at Duke University.

DR. SCHMIDT: I am Jimmy Schmidt, private practice, Houston, Texas.

DR. WILLY: I am Mary Willy. I am a Senior Risk Management analyst and the team leader epidemiologist in the Office of Surveillance and Epidemiology at the FDA.

DR. KARWOSKI: Good morning. I am Claudia Karwoski. I am the Risk Management Team Leader in the Office of the Surveillance and Epidemiology at FDA.

DR. WALKER: Good morning. I am Susan Walker, Director of the Dermatology and Dental Products Division at FDA.

DR. BEITZ: I am Julie Beitz, Director of Office of Drug Evaluation III in CDER, FDA.

DR. KWEDER: Good morning. I am Sandra Kweder, the Deputy Director of the Office of New Drugs in CDER at FDA.

DR. BIGBY: Thank you.

There is an opening statement that I am supposed to read. For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

Thank you.

I will turn the meeting over to Sohail.

Conflict of Interest Statement

LCDR MOSADDEGH: I have an addition to

that statement plus I will be reading the Conflict of Interest.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that any conversations about today's topic take place in the open forum of the meeting and not during breaks. We are also aware that members of the media are anxious to speak with the FDA about these proceedings.

However, like the Advisory Committee members, FDA will refrain from discussing the details of this meeting with the media until its conclusion. For the convenience of the media representative, I would like to identify the FDA press contact, Mr. Christopher Kelly. If you are present, if you could please stand.

Finally, I would like to remind everyone present to please silence your cell phones and pagers if you have not already done so. We look forward to an interesting and productive meeting.

Thank you.

I will be reading the COI Statement now.

The following announcement addressees the ius of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interest reported by the Committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest with the following exceptions.

In accordance with 18 U.S.C. 208(b)(3), Dr. Peter Gross has been granted a waiver for his being on a speakers bureau for an affected firm on unrelated issues. Dr. Gross receives less than $10,001 per year.

Waiver documents are available at FDA's Dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room at the FDA information table.

In addition, copies of all the waivers can be obtained by submitting a written request to the

Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

With respect to FDA's invited industry's representative, we would like to disclose that Dr. Peter Kresel has been invited to participate as a non-voting industry representative acting on behalf of regulated industry. Dr. Kresel's role at this meeting is to present industry interest in general and not any one particular company. Dr. Kresel is employed by Allergan, Incorporated.

In the event that the discussion involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from the discussion and their exclusion will be noted for the record.

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

Thank you very much. Dr. Bigby?

DR. KRESEL: Excuse me. This is Peter Kresel. I would like to correct, for the record, I am not employed by Allergan.

LCDR MOSADDEGH: Thank you.

DR. BIGBY: I would like to turn the floor over to Dr. Walker to give the charge to the Committee.

Charge to the Committee

DR. WALKER: Thank you very much, Dr. Bigby. Welcome to the Committee. Our thanks to all of you present who have taken the time to be with us this morning. Our thanks must include and acknowledgment of the time that the Advisory Committee members have spent reviewing the background package materials in preparing for today's meeting.

The purpose of today's meeting is to update there committee on risk-management activities isotretinoin drug products since the implementation of the iPLEDGE Program in 2006.

The iPLEDGE Program is the most rigorous Risk Management Program approved by FDA requiring

mandatory registration of patients, physicians, pharmacies and wholesalers. iPLEDGE is designed to fully educate patients on the teratogenic risks of isotretinoin therapy and to capture as accurately as possible the outcomes in women of childbearing potential.

As discussed in the charge to the Committee at the last meeting, I want to note that, although the goals of this program are that no woman should begin isotretinoin therapy if pregnant and that no pregnancy should occur while a woman is taking isotretinoin, the agency is very cognizant of the fact that setting a zero goal as a metric for something that depends on human behavior for success is probably not possible to attain.

It is good to set that goal, but many of these issues are not within the control of manufacturers, physicians or the agency. Nonetheless, we have worked intensely and tirelessly with the sponsors of isotretinoin to ensure that the iPLEDGE Program, itself, and all participants are doing their part to meet the

goals.

While it may be impossible to actually meet a zero goal, we think it is important to strive to attain this important goal. The information now available from the first year of iPLEDGE sets the foundation for future evaluation of the iPLEDGE Program.

While there may be inevitable comparisons of the iPLEDGE 1-year data to data obtained from prior risk-management programs for isotretinoin, these comparisons are hampered by challenges in interpreting data from non-mandatory programs.

These previous programs did not definitively capture either the total number of females of childbearing potential receiving isotretinoin therapy or the total number of woman who became pregnant.

In previous programs, only a subset of woman completed the voluntary survey about contraceptive use in program compliance whereas, with iPLEDGE, this information is obtained from all patients.

One of FDA's standards for risk-management programs is that these programs must be periodically evaluated for effectiveness. We intend to update the joint committee as data accrues. This will allow an appropriate comparison of future data to the baseline data being presented to the committee today.

So, for today's deliberations, we are seeking your input in two specific areas. Firstly, the sponsor has proposed three modifications to the established time frames within which a patient must actually go to the pharmacy and pick up their prescription. Under the current system, patients who arrive at the pharmacy outside the allowable window will be sent away without their medication.

The specific proposed changes will be described in the presentations during the first half of the morning. The agency feels these changes would result in enhanced flexibility of the program, reduced interruptions in treatment and reduced burden to participants, especially for those not at risk for pregnancy.

We are seeking your consideration and recommendations concerning these proposed modifications.

Secondly, the assembled data from the first year of the program will be presented by the sponsors in the second half of the morning followed by some perspectives from FDA on the iPLEDGE pregnancy registry and educational programs.

We are seeking your consideration and recommendations regarding the pregnancy registry and any additional comments the Committee may have to address the risk-management functions of the iPLEDGE Program.

Again, when the iPLEDGE Program was developed, the transition from a voluntary system to a mandatory program made it clear that assessing how well the goals were met would need to be on the basis of the program, itself; in other words, comparisons to older programs would be difficult at best.

What will be presented, today, is time-point zero which will serve as a foundation

for all future comparisons and allow us to assess areas where the program can be strengthened to meet its goals.

We look forward to your discussions. Thank you very much.

DR. BIGBY: I would like to turn the floor over to Dr. Diglisic to discuss the regulatory history of isotretinoin and program changes.

Regulatory History of Isotretinoin and Program Changes

DR. DIGLISIC: Good morning.

[Slide.]

Today, I will present the regulatory history of isotretinoin, pregnancy prevention program and proposed changes.

[Slide.]

Accutane was approved in 1982 for the treatment of severe recalcitrant nodular acne. Genetics entered the market in 2002.

[Slide.]

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous follicle

and can range in severity from mild to severe. Severe nodular acne is characterized by the presence of the nodules, edematous tender lesions, which may be suppurative or hemorrhagic. Nodules can persist for a month and resolve with permanent scars.

This is a picture of a patient with severe nodular acne before the treatment with isotretinoin.

[Slide.]

And after the treatment with isotretinoin.

[Slide.]

This is another picture of the patients with severe nodular acne.

[Slide.]

The single course of the therapy, 15 to 20 weeks, results in complete and prolonged disease remission in many patients like in this one.

[Slide.]

Isotretinoin remains the only approved drug for this indication.

[Slide.]

However, isotretinoin is highly teratogenic, contra-indicated in the pregnancy and labeled as pregnancy Category X. Risk management, at the time of original approval, was limited to labeling. In 1984, a box warning was added recommending pregnancy testing prior to Accutane initiation and the use of contraceptives for a month prior to therapy.

[Slide.]

Over the years, the risk issue, teratogenicity, was the subject of multiple advisory committee discussions leading to subsequent additions to the Risk Management Program including "Dear Doctor" letters, red warning stickers and, in 1988, the sponsor introduced the Accutane Pregnancy Prevention Program.

The program stated in the content of the labeling added new education and reminder tools, patient informed-consent form and voluntary patient and prescriber surveys.

[Slide.]

In September, 2000, the Dermatologic and

Ophthalmic Drug Advisory Committee reviewed the adequacy of the Pregnancy Prevention Program for Accutane and concluded that the program was not sufficiently effective in minimizing pregnancy exposure during the isotretinoin therapy.

DODAC, therefore, recommended improvement on the Accutane Pregnancy Prevention Program by augmentation of the patient education, mandatory registration of all patients and prescribers, implementation pregnancy registration and linkage of prescription dispensing to negative pregnancy testing.

[Slide.]

In response to DODAC recommendations, a sticker-based program System to Manage Accutane-related Teratogenicity, SMART, was developed by the sponsor and approved by FDA in October, 2001 followed the similar programs for genetic products.

SMART added requirements for the second pregnancy test, use of two forms of contraception and a new reminder tool, yellow qualification

stickers. All patients were required to sign general informed-consent forms and patients were required to sign second pregnancy-prevention informed-consent forms.

The Medication Guide is dispensed with the drug and voluntary patient surveys continued.

[Slide.]

In February, 2007, the Drug Safety and Risk Management Advisory Committee in a joined meeting with the DODAC convened to review the data from the first year following SMART implementation. The Committee recommended the strengthening and consolidation of the isotretinoin Pregnancy Prevention Program to include; registration of all patients prescribers and pharmacists, tighter linkage of the pregnancy testing to prescription dispensing, implementation of pregnancy registry and participation of all manufacturers in a single risk minimization action plan.

[Slide.]

Following DODAC and this recommendation, a new single program for isotretinoin called iPLEDGE

was approved on August 12, 2004. The essential element of the iPLEDGE Program is the performance-linked access system called Plus.

Plus tightly links the dispensing of isotretinoin to the documentation of monthly counseling for all patients, documentation of monthly pregnancy testing for female patients of childbearing potential, demonstration of comprehension by answering monthly questions, prescriber and patient identification of contraceptive methods chosen, and pregnancy registry for root-cause analysis to identify underlying causes behind fatal exposure.

[Slide.]

Access to the iPLEDGE system is restricted to registered prescribers, pharmacists and patients to ensure that the only prescribers registered and activated in iPLEDGE can prescribe isotretinoin, only pharmacists registered and activated in iPLEDGE can dispense isotretinoin and only patients, both males and females, registered and qualified in iPLEDGE can receive isotretinoin.

[Slide.]

After approval, stakeholder registration, begun in September, 2005, patient enrollment opened in late December, 2005 and transition from the previous program to iPLEDGE was completed on March 1, 2006 when the iPLEDGE Program became mandatory for all users.

[Slide.]

Male and female patients not of childbearing potential must be registered in iPLEDGE initially which is done by prescriber and the prescriber must interact with the iPLEDGE system each month to confirm that the patient understands the iPLEDGE Program requirements such as, do not give blood, do not share isotretinoin.

All patients have a specific period of time in which they can fill and pick up their prescriptions. This is called the prescription window. The prescription window is 7 days and starts at the day of the office visit. Prescriptions that are more than 7 days beyond the date of the office visit will not be authorized by

the iPLEDGE system and the patients will be locked out for an additional 23 days after which a patient will be required to start the process all over again by visiting the healthcare provider.

[Slide.]

Qualification of a female of childbearing potential is more complex and differs in four ways from the qualification process under SMART. First, in iPLEDGE, the second confirmatory and each month's follow-up pregnancy test must be preformed at a certified laboratory.

Second, the prescriber must confirm each month in the iPLEDGE system that contraception counseling has occurred.

Third, both prescribers and patients must enter in the iPLEDGE system the primary and secondary form of contraception that the patient had selected.

Fourth, the patient must correctly answer the questions intended to bring forth the key messages about the iPLEDGE Program.

[Slide.]

During implementation, issues and concerns from stakeholders including the prescriber community emerge such as slow registration and call-center overload. Additionally, many patients had prescriptions denied and treatment postponed because the iPLEDGE system was programmed to lock out the patients for an additional 23 days if they did not fill their prescription within 7 days of the office visit.

[Slide.]

These charts provide the projected number of isotretinoin dispensed from the June '05 to June '07. As you can see from the charts, the total prescriptions dispensed for isotretinoin in January, '06, was over 97,000 dropped down to a little bit above 62,000 in March '06 when the iPLEDGE Program was implemented. The number of prescriptions was slowly rising reaching 91,000 in March, 2007.

Before iPLEDGE was implemented, there was a split, 50:50, between prescriptions for male and female patients. After the iPLEDGE was

implemented, the prescription for female patients accounted for only about 39 percent of all prescriptions written. Over time, the gender gap closed somewhat and, in April, May and June of this year, 46 percent of the prescriptions were written for female patients.

[Slide.]

This chart represents the projected number of the patient age of between 15 and 45 years receiving the isotretinoin prescription from June '05 to June '07. The patient population between 15 and 45 actually represents over 90 percent overall for isotretinoin patient volume.

The number of the male patients receiving isotretinoin prescriptions before the iPLEDGE Program was implemented was roughly about 40,000 per month. After the iPLEDGE implementation, the numbers of the patients dropped down and then slowly returned back and now they are at the level they were before iPLEDGE was implemented.

For the female patients, the number of the female patients receiving prescriptions was about

36,000 in January '06 and then dramatically dropped down below 20,000 for March '06 when iPLEDGE became mandatory for the users. The highest number of prescriptions now was these late couple of months which is about 32,000.

[Slide.]

Based on the stakeholder and feedback, the sponsor removed the 23-day lockout for males and females not of childbearing potential in October, 2006. This action did not require labeling changes, gave more flexibility to this subset of the patients and reduced interruptions in the treatment and the burden to the stakeholders.

[Slide.]

The agency is currently considering this proposed revision; removal of the 23-day lockout for females of childbearing potential, linkage of the 7-day prescription window for female patients of childbearing potential to the date of specimen collection for the pregnancy testing rather than the office visit and extension of the prescription window from 7 days to 30 days for male and female

patients not of childbearing potential.

[Slide.]

These changes are intended to enhance the flexibility of the program, reduce the interruptions in the treatment and reduce the burden to stakeholders. However, the agency anticipates that these changes would not produce the rigor of the iPLEDGE the risk minimization program.

Thank you for your attention.

DR. BIGBY: I would now like to recognize Dr. Southorn who will discuss the design of the iPLEDGE Program and proposed programmatic changes.

Design of the iPLEDGE Program

and Proposed Programmatic Changes

DR. SOUTHORN: Good morning.

[Slide.]

My name is Bonnie Southorn. I work at a company called Genpharm which is one of the sponsors of the iPLEDGE Program and I am speaking to you today on behalf of all of the sponsors of the iPLEDGE Program. I would just, first of all,

thank the FDA for inviting us today to give you this presentation on the program and to share with you our Year 1 findings.

[Slide.]

I'm going to give you a bit of an overview of iPLEDGE and then I am going to turn it over to James Shamp from Covance who will discuss the program's design and the Phase 2 enhancements that you have just seen an overview of. Following a short Q and A, then Dr. Daniel Reshef from Hoffman-LaRoche will present the Year 1 pregnancy data.

[Slide.]

Our objectives at this meeting are to give you an update of the progress of the iPLEDGE Program including our enhancements, to inform you of the next steps in timing for the Phase 2 implementation and to present our data.

[Slide.]

Just to remind you again, there are four products on the market right now, the innovator, Accutane, which has been on the market since May

'82, and three generics sponsored by Genpharm Ranbaxy and Barr Laboratories. They were approved between November, '02 and April, '03.

[Slide.]

Again, to remind you of the public-health goals; no woman who is pregnant should receive isotretinoin therapy and no woman should become pregnant during or for one month after receiving isotretinoin therapy.

[Slide.]

The basis for the iPLEDGE RiskMAP. iPLEDGE [sic] is a known teratogen. It was approved in August '05 in the supplement under Subpart H with a restricted distribution program and that restricted distribution program is an enhanced risk-minimization action plan designed to minimize drug exposure during pregnancy.

[Slide.]

Just a quick comparison, again, between the previous RiskMAP and the iPLEDGE Program. Previously, as was stated earlier, it is a voluntary program. Now we have a mandatory program

for all participants wishing to use the product. We now have essentially 100 percent data capture of prescriptions as well as pregnancies through the new program. We can now, for the first time, have the patient denominator, the number of people that are actually taking the product.

It is a comprehensive program. All stakeholders using the product are involved and enrolled and we have, for the first time, a single centralized pregnancy registry for all pregnancies reported on this drug which allows us to look toward root-cause analysis and mandatory reporting of pregnancies as well as to conduct a more uniform lost-to-follow-up process to ensure that we get as complete a dataset as possible.

[Slide.]

The previous programs relied on a yellow sticker being presented to the pharmacy in order to qualify a patient to receive prescriptions. The current system is a performance-linked system where the pharmacy actually checks on the system and really has assurance that the pregnancy testing

required was done as well as the pregnancy testing now must be done in a CLIA-certified lab so there is more reliability of the actual results.

[Slide.]

A recent history of the program: in 2004, we came to this committee and proposed a registry program to you. This registry program was a joint program of all four sponsors working together for all isotretinoin products. It included a registry of prescribers, pharmacies and patients and a single centralized pregnancy registry.

In general, the committee agreed with our proposal and gave us some additional feedback that all healthcare professionals should be registered, we should have some comprehension testing of our education materials as we develop the program, we should have a mandatory patient follow-up survey and that the launch of the program should not be delayed by conducting a pilot program or any sort of cost analysis.

[Slide.]

As was mentioned earlier, the FDA approved

the iPLEDGE Program in August, 2005 and there was a transitional period which started patient registration right at the end of '05, beginning of '06, and, in February 10, '06, we, again, came before the committee to give you an overview of the program that we had built that was in the process of being launched.

We received some additional operational feedback from stakeholders at that time. As of March 6, '06, participation for dispensing and all aspects of the program became mandatory.

[Slide.]

In February of this year, a supplement was submitted to the FDA proposing the Phase 2 changes that you will hear more about this morning. We have been exchanging some responses and comments with the FDA and, currently, the status of those enhancements is that we are doing some additional system design and programming, testing for the next release.

We are in the process of updating the educational materials to reflect the changes and

our target date for launching this is sometime after today's committee meeting and the FDA approval of that supplement. So we look forward to your recommendations this morning.

On June 1, the FDA informed us of this meeting and asked us to come and present to you our data as well as the overview of the program and the enhancements. I will now turn it over to Mr. James Shamp from Covance who will give you a little bit more detail on the program.

MR. SHAMP: Good morning.

[Slide.]

My name is Jim Shamp. I work for Covance.

[Slide.]

Looking at who is part of iPLEDGE, iPLEDGE is a performance-linked access system unprecedented in size and scope requiring the registration of all stakeholders. As a performance-linked access system, it required specific interactions from the stakeholders with the system. Looking at these interactions, the manufacturers can only ship isotretinoin to a wholesaler that is registered in

iPLEDGE. The wholesaler can only ship and sell isotretinoin to a pharmacy that is registered and activated in iPLEDGE.

A pharmacy must authorize every prescription before dispensing through iPLEDGE. They can only authorize and dispense to a patient that has seen a prescriber, been registered and completed their activities in the iPLEDGE system and the prescriber must register these patients, provide the counseling to these patients.

For females of childbearing potential, they also have to enter in their two forms of birth control as well as entering the pregnancy results.

[Slide.]

iPLEDGE is made up of several major components. Interactions are performed through either a website or through an automated phone system, also known as an IVRS. Education materials, which I believe you have today, are provided to prescribers, patients as well as pharmacies. The education materials, as well as the IVRS prompts are provided in Spanish and

iPLEDGE also includes a pregnancy registry.

[Slide.]

Talking a moment about the education materials, we did perform a qualitative and quantitative testing of these materials in 2005 before we rolled out iPLEDGE at the end of 2005. The testing was conducted in 26 geographical locations and included 500 females of childbearing potential.

The results of this testing was that the program guide for the females of childbearing potential were successful at communicating the key information about the program and the birth-control workbook was also very successful at communicating some very specific points.

The first one is the necessity of using two forms of birth control. Over 99 percent understood that two forms are recommended and 9 out of 10 them said they would personally use two or more forms. They also recalled the importance of taking birth-control pills every day and the majority said they would take immediate action if

they had unprotected sex or became pregnant.

[Slide.]

So, looking at the specific activities of these stakeholders, wholesalers have to register initially as well as every year that they wish to participate in the program. They can only distribute FDA-approved products. They can only provide drug to a pharmacy that is registered and activated in the iPLEDGE Program. This is verified by the wholesaler by receiving a daily list of registered and activated pharmacies.

Prescribers have to register initially and they also have to activate that registration initially as well as every year they wish to participate. They have to register all patients in the program. They obtain consent forms from all patients, one from all patients and an additional second consent form for females of childbearing potential. That consent form is specific to birth defects.

They have to provide counseling to the patient, to the female patients of childbearing

potential, about birth control as well as all patients about not donating blood or sharing their drug. They have to confirm that counseling in the system and they have to enter the females of childbearing potential's choices of contraception in the system as well as the pregnancy-test results for them.

[Slide.]

Pharmacies have to register initially and they also activate their registration initially and every year they wish to participate. They have to designate a responsible site pharmacist that is responsible for all the actions of that pharmacy in iPLEDGE one of which is they must train all pharmacists in the process of authorizing a prescription through iPLEDGE.

Pharmacies cannot dispense after the prescription window as ended, after the 7-day window, and they can dispense no more than a 30-day supply at any one time.

[Slide.]

So now you have seen the activities for

the prescriber, the wholesaler and the pharmacy. We will talk a little bit about the patients now.

All patients must be registered. They have to sign the consent form. They have to schedule monthly visits to see their prescriber. They should not donate blood nor share their drug and they must pick up their prescription in the 7-day window.

Additionally, females of childbearing potential have some additional requirements. They have to sign the second consent form. They have to have monthly pregnancy tests performed in a CLIA-certified lab. They have to enter their monthly contraception choices as well as answer comprehension questions.

[Slide.]

So now we have seen the activities that the stakeholders must perform. Now we going to look a little bit at what happens if one of these stakeholders does not complete one of their activities. These are the prescription denials.

[Slide.]

Looking at females of childbearing potential for the first year, the two most common reasons for denial were that the female attempted to fill her prescription at a pharmacy in her 7-day window without answering her comprehension questions. The second most common is that she attempted to fill the prescription in the 7-day window and the prescriber had not entered the pregnancy results for that month.

Looking at males and females of non-childbearing potential, the two most common reasons for them is that they attempted to fill their prescription and the prescriber had not confirmed their counseling in the system and the second most common was that they waited until after the 7-day window had expired before they attempted to get it filled.

[Slide.]

Now, we have seen the stakeholder's activities. What happens if the stakeholders don't complete those activities when they try to fill a prescription. Now we are going to talk a little

bit about what happens if one of the stakeholders operates outside of the iPLEDGE system and that is our noncompliance process.

[Slide.]

The process begins with the recognition of a suspected noncompliance activity. We start the process with sending a traceable letter to the stakeholder identifying this activity. We follow up that up with a phone call to the stakeholder. We discuss this suspected noncompliance activity. We discuss corrective action and take the opportunity to provide additional activity to that stakeholder on the iPLEDGE processes.

Once that is complete, we do provide follow up on the stakeholder to confirm that they have implemented the corrective action. In the case that they have not or if the noncompliance activity is considered severe, we will deactivate the stakeholder from iPLEDGE meaning they cannot participate in iPLEDGE anymore.

For the first year, we had two deactivations for prescribers and one deactivation

for a pharmacy

[Slide.]

Some of the noncompliance activities are reportable to the FDA. There are two specific. The first is if a wholesaler shifts isotretinoin to a pharmacy that is not registered and activated or to another wholesaler who is not registered in iPLEDGE and the second is if a pharmacy dispenses isotretinoin and they are not registered and activated in iPLEDGE.

In addition to these two 15-day reportables, the sponsors may also choose on a case-by-case basis. If the noncompliance activity is severe enough, they may also report that stakeholder as a 15-day reportable to the FDA.

[Slide.]

I will now talk about the proposed Phase 2 changes and, as I do, it is important to understand that risk management is an iterative process of assessment, minimization and evaluation. As part of this iterative process, RiskMAPs are evolving programs and, to that end, we are proposing the

following changes.

[Slide.]

Since iPLEDGE's inception, we have received feedback from various places. We have received feedback from the call center through observation of the prescription denials, stakeholder interactions, through our Scientific Advisory Board, the FDA, professional organizations such as the Academy of Dermatology, the Healthcare Distribution and Manufacturers Association and the National Association of Chain Drugstores.

We have also received some feedback from the sponsors. We commissioned a useability test in the fall and received feedback from that testing of the website.

[Slide.]

Phase 2 has four proposed label changes. The first is to remove the 23-day lockout for females of childbearing potential. This 23-day lockout was removed for the males and females of non-childbearing potential in October. We are now proposing to eliminate it for the females of

childbearing potential.

There is one exception to this. If the females misses here first prescription, she is required to wait 19 days between her two pregnancy tests. That is a requirement that comes out of the package insert that first prescription must be proceeded by two pregnancy tests at least 19 days apart. So, if she misses that first one, we do lock her out and require that second pregnancy test 19 days later before she can start the process over.

Otherwise, in order to start the process, she and the prescriber must both complete all of the requirements again in iPLEDGE to qualify for another prescription.

The second change is to start the 7-day window on the collection date of the pregnancy test. Today that window starts on the date the prescriber confirms the patient in the system and we are changing that to start on the date of pregnant collection.

One of benefits of this is that it is more

conducive to current office practices. It does allow the prescriber to obtain all blood work before seeing that patient. It also combines the actions of the prescriber. Today, it takes two actions from the prescriber to qualify a patient. The prescriber must confirm the patient in the system and subsequently enter the pregnancy results. With this change, we are combining the two of those into one step.

The next two proposed changes were both requested from the FDA. The first is to extend the 7-day window for males and females of non-childbearing potential from a 7-day window to a 30-day window. This would provide additional time for these patients to get their prescriptions filled. As you will recall from a previous screen, this was the second-most-common denial reason for these patients.

The last proposed label change is to allow a male latex condom with and without spermicide. Today, a male latex condom is allowed with spermicide only and this change is in line with

FDA, CDC and WHO guidelines.

[Slide.]

I am now going to compare the current 7-day window for a female of childbearing potential with what the 7-day window will look like after these changes have been implemented.

As we see here, the window starts today with the office visit. After that, the patient must have her pregnancy test. The prescriber must then enter the pregnancy-test results and the patient has to enter her comprehension questions.

Once those activities are complete, the patient can proceed to the pharmacy and have her prescription authorized in iPLEDGE and she must do that before the 7-day window expires. After it expires, she is locked out for another 23 days before she can start this process again.

With the changes that we are proposing, the 7-day window would now start on the pregnancy test date. The office-date visit become flexible. It can occur before or after the pregnancy test. The prescriber then confirms the counseling and

enters the pregnancy test into the system as one step.

Once that is complete, the patient may answer her questions in the system and then proceed to the pharmacy to get her prescription authorized. She still must do that before the 7-day window expires and, if she misses the window, she is no longer locked out. She can go back on Day 8 and start another process and qualify for another prescription.

[Slide.]

In addition to the label changes, we are also proposing some enhancements. These enhancements are to create more flexibility in entering data and getting additional data out of the system. The first change is robust, enhanced patient status display. This display goes to both prescriber and the females of childbearing potential. I will talk more about this in a moment.

We are also enhancing the messages that are provided back to the stakeholders. As an

example, today, if a prescription is denied because the patient did not answer her comprehension questions, we simply tell the pharmacy, this prescription is denied and you must have the patient call the prescriber.

With these changes, we will tell the pharmacy that the prescription is denied and please tell the patient she must answer her questions before she can get her prescription. So we provide much more information to the users.

The last set of changes we are making in this Phase 2 are navigational-type changes. This is to enhance the way the stakeholders enter data through the system making it more conducive to how it would work on a website and more conducive to their office practices.

[Slide.]

I know you probably can't read the screen, but allow me to try to tell you what is on this. This is the prescriber's version of the patient-status page. What it does provide is a graphical representation in a calendar view of the

patient 7-day window. From this screen, the prescriber and the patient can tell exactly where they are, what they need to do, when they need to do it by and, if it wasn't done, the end result.

In this case, you can see the seven green boxes is the 7-day window. This one happens to be expired. If you can tell, there are X's in the windows. An X means that day has completed. It has passed.

We can tell from looking at this that this was the first day. This was the first of the window. This is the first day the patient could answer her comprehension questions. She did that on the 10th, I believe. On the 10th, it now tells her that she may pick up her prescription.

In addition to the text that you see on here, each day has a more text link which means you can select that link and it provides more information about the activities that need to be performed and when they need to be performed by.

In addition, the prescriber and the patient can perform most of these activities

directly off the screen. In this case, the patient is ready to be confirmed for her next prescription and there is a link right here that tells the prescriber, click here to confirm this patient.

In addition to just the 7-day window, it also provides information for when that patient can start her next 7-day window. As I just explained, the 7-day window screen, we are eliminating the 23-day lockout so, at the end of this patient's 7-day window, she may proceed the next day to begin the process again. In this case, it says this is the first day a patient may have the next pregnant test.

The additional information provided on the screen will assist the prescriber in determining the patient's compliance in iPLEDGE by providing all this information as well as indicating if the prescription was filled. In this case, this patient filled her prescription on the 10th, which is that day right there.

[Slide.]

So, in summary, iPLEDGE is an integrated

program that supports the public-health goals. There are both label change and program enhancements in Phase 2 that has been submitted to the FDA. These changes will increase the user's capability to meet to program requirements.

We have some additional planned activities to meet a Phase 2 schedule. Right now, we are producing new educational materials. These materials have been updated to reflect these changes in iPLEDGE. We will be communicating all these changes to all stakeholders participating in iPLEDGE.

We are distributing these new educational materials to all participating stakeholders and we are currently hiring and training additional call-center staff to handle what we think will be an increased number of calls in to the call center as a result of the Phase 2 changes.

As Bonnie Southorn said earlier, the launch date of Phase 2 is pending comments from this committee as well as approval from the FDA.

I will now rejoin my colleagues and we

will entertain your questions.

DR. BIGBY: Unless somebody at the table has a big objection, my preference would be to keep going with the presentation and hold all the questions until the end. Is that okay with the committee?

So I would like to now recognize Dr. Reshef who is going to talk about the iPLEDGE Program one-year update.

iPLEDGE Program--One-Year Update

DR. RESHEF: Good morning, everybody.

[Slide.]

I am honored to be here. I am Dan Reshef from Hoffman-LaRoche. I was asked to present the Year-1 iPLEDGE data which we will do.

[Slide.]

This morning, we will go through some of the descriptions of the interactions that females of childbearing potential have with the system. I will proceed to the pregnancy data and share with you some initial observations regarding patient knowledge and patient behavior.

[Slide.]

So, to set the stage, I would like to walk you through the interactions that take place between a potential patient interested in treatment with isotretinoin and the iPLEDGE Program.

[Slide.]

This patient will initially entertain a registration visit. At that time, it will be determined if she is of child-bearing potential. A screening pregnancy test is taken and she would sign an initial informed consent.

There is an interaction, an educational interaction, with the prescriber and the iPLEDGE educational kit including the iPLEDGE I.D. card are being offered to the patient. Patient demographics are entered into the system and system enforced 30-day wait is beginning at this point.

[Slide.]

The next stage is the patient confirmation visit. At this time, two forms of contraception that a patient is choosing to use and is committed to use are being recorded. There is further

patient education that takes place with the medical practitioner.

Laboratory pregnancy tests are conducted and the patient receives an initial prescription. At that point, the 7-day window that has been described kicks in and the patient also is required to sign a more detailed second consent form.

[Slide.]

The following step is the interactions that take place between the patient and the system. That is composed of a documentation of the chosen method of contraception, a baseline survey that each females of child-bearing potential is required to complete, as well as a set of questions that capture the comprehension of the educational materials. At the same time the prescriber enters the pregnancy-test results that are being received into the system.

[Slide.]

The following step is actually taking place at the registered pharmacy. The pharmacy would verify that the prescription is an authorized

prescription, would provide the product information, the quantity dispensed and the day of supply. It would obtain an RMA number which is the absolute condition for actually filling the prescription, would provide the patient with a medication guide and would dispense the medication, provided that it occurs prior to the do-not-dispense-after date; in other words, that it is still in the 7-day window.

[Slide.]

Now the patient can actually start the treatment of isotretinoin. 30 days elapse and if she, together with the prescriber, agree that treatment will continue, she would return to the patient confirmation visit. So she is back at this step and everything listed in this box that I have described takes place again.

However, if the therapy was completed, there are two additional very important steps. The woman has agreed to undergo an additional pregnancy test at the end of the therapy and 30 days later there is another pregnancy test one month after

completion of the therapy.

[Slide.]

I would like to take you on to the pregnancy registry. The pregnancy registry for isotretinoin has a number of objectives: first and foremost to determine the exposure status of each reported pregnancy; to document the outcome of each reported and exposed pregnancy; to determine the root-cause analysis for each exposed pregnancy; to determine the patient knowledge, attitude, behavior regarding the iPLEDGE requirements which are fairly extensive; to determine the most likely reported cause of pregnancy as assessed both by the healthcare practitioner and the patient, herself; to provide pregnancy data in periodic reports to the FDA; and, basically, to develop a centralized database for all isotretinoin pregnancies reported.

[Slide.]

Let's look at the pregnancy registry. There are three sources of input into the root-cause analysis. The information that comes into the pregnancy registry may come from the

patient, herself, or may come from the prescriber. In any case, the prescriber assessment on the reason of pregnancy takes place and the Year 1 process requires a written consent to proceed and complete the root-cause-analysis forms which are part of the root-cause analysis.

The root-cause analyses really take into consideration input from these three sources; the prescriber, the patient and the analysis form that the patient completes.

[Slide.]

Now, I will move on into the pregnancy data that we have upon conclusion of Year 1 of iPLEDGE.

[Slide.]

It is very important to remember--based on the detailed description of the processes I have outlined for you, it is important to realize that at every stage in the process, there are a number of patients that have completed that stage and this number may change from stage to stage.

To clarify this, I would like to walk you

through this important table. The total number of males registered into iPLEDGE was 135,507. Of these males that registered, 132,000 received at least one RMA. The total number of females that registered into the system was 132,708 of which 102,680 have proceeded to the later stage in the process and received at least one RMA.

Looking at this group of female patients, 91,894 were females of child-bearing potential that have received at least one RMA and 10,786 were females of non-child-bearing potential that have reached the stage of having received at least one RMA.

The reason this number of bolded is that we think that this is the closest denominator estimating the number of female patients of child-bearing potential that actually had an okay to proceed and obtain the drug.

[Slide.]

The way pregnancies are classified in the Year 1 data relies on these three parameters; the patient must have been a registered patient in

iPLEDGE, the initial report was received by March 31st of 2007, and the conception date occurred before February 28th of 2007.

Just to remind you, the total number of females of child-bearing potential who received at least one RMA in the Year 1 of the program was 91,894. From this group, we have, in the isotretinoin pregnancy registry, a total number of 122 reported pregnancies.

[Slide.]

Now, we have heard this morning and we all know that isotretinoin is a teratogenic agent. It is important to attempt to capture the relationship, the time relationship, between the conception date and the treatment. This is what you can see on this table.

Here is the total number of 122 reports of pregnancy from this 91,894 FCBPs. Ten women started treatment and the conception date occurred prior to the treatment initiation. 78 pregnancies occurred during isotretinoin treatment and 8 pregnancies occurred within the 30-day window after

isotretinoin treatment was completed.

This relationship between treatment and the conception date could not be definitely assessed in 26 pregnancies in which we know that 15 had an indeterminate exposure to the drug to begin with.

[Slide.]

One of the most important questions that we are struggling with is is the comparison between the very small group of pregnant women and the large group of non-pregnant women. You will see a number of tables that try to list these two groups side-by-side.

On this slide, you can see the age distribution of the 97,886 non-pregnant women for which we have that information. This is a larger number because this information is collected earlier, before the RMA stage. We can see the distribution of the entire females of child-bearing potential group.

Looking at the 122 pregnant women, it is important to note that about 80 percent of them are

above age 20 and about 20 percent are in the younger age band.

[Slide.]

Let's look at the reasons for pregnancy as reported by the prescriber and by the patients in the first year.

[Slide.]

We have follow up on 87 of the 122 pregnancies that originated from the prescriber. Here is the breakdown. The reason that prescribers have attributed to the pregnancy was contraception failure in 23 instances, not using two forms of birth control in 16 instances, failure to use contraceptives on the day of conception 14 times, unsuccessful at abstinence 14 times and using an ineffective contraception once.

In addition, I would like to point out to all of you that these reasons are not mutually exclusive in the form. The way the information is collected allows for more than one choice. The unknown, and actually, 31 of these 42, were pure unknown and there is such a choice in the

information form. The remaining, the difference, would be unknown and another reason.

[Slide.]

We also have information from the women that became pregnant. This information, again, allows for the women to provide their input. Interestingly, the most common reason for pregnancy that the women have identified was not using two forms of birth control followed by contraceptive failure seven times, missing was six times, unsuccessful at abstinence, twice.

[Slide.]

A full analysis of the root-cause forms was not conducted yet. It is really early in the system, but we have some initial observations that point to some interesting behavioral hints that we can already begin to see.

Most patients reported were counseled about the risk of birth defects. They responded, "Yes, I was counseled about the risk." Also, most of them responded that they were instructed not to become pregnant. Interestingly, most patients were

college graduates or had some college education. One would think that these are young women that have comprehension skills.

Nearly half of the patients reported using one form or no form of birth control when having sexual intercourse during the month of conception, one-half of the patients that provided answers.

[Slide.]

A number of improvements to increase the collection of root-cause-analysis forms have been implemented. In Year 2, if the pregnancy is reported by the prescriber, there is no direct patient contact after notification of her pregnancy by the prescriber. But now, based on verbal consent at the initial contact, we shifted to completely the RCA form right away here and now and seized this opportunity to obtain valuable information from that patient.

When the pregnancy is reported by the patient, we would obtain verbal consent at the initial contact again to attempt to proceed with the root-cause-analysis form as soon as possible.

This is followed by the primary prescriber for additional information.

There is one important change that is considered by the IRB at this time. We realize that, oftentimes, the primary healthcare provider may not be the person that has relevant information about the pregnancy. Oftentimes, this would be another healthcare provider like an OB-GYN. So, upon verbal consent, we would like to be able to proceed and contact that other healthcare provider that may provide valuable information.

[Slide.]

I would now like to share with you some of the Observations of Patient Knowledge/Behavior part of the problem including the baseline survey, the comprehension and the contraception choices made.

[Slide.]

The baseline survey occurs prior to therapy, of course. It is comprised of eight questions. The patient logs into the Answer Questions on the web or on the interactive voice system.

The content of the survey covers four areas; was the patient told to avoid pregnancy, has the patient received the educational materials, has the patient reviewed the education materials and from whom was birth-control counseling received. This survey is presented before the comprehension questions.

The bottom line I would like to highlight to you is that we did not see any apparent difference between the non-pregnant and the pregnant patients in this part of the program but I would like to share with you the details.

[Slide.]

So, on this table, you can see a comparison again, as you have seen before, of the non-pregnant group which is a large group and the pregnancy females.

What is summarized in the table are the positive responses to each one of the questions. In fact, there is no difference. I would like to point out that the percentage of both females that became pregnant and the females that were

non-pregnant that responded positively to these questions are very, very high, 95, 96, 97, 99 percent, 99.7 percent. And there is really no difference.

There is a puzzling difference in the sense of higher, slightly higher, percentages of the women that watched the two videos that are available and we cannot explain this observation at this time.

[Slide.]

The doctor offered to refer for birth-control counseling to another healthcare provider in 50 percent of the non-pregnant and in 54.9 percent of the pregnant women. To the question, from whom did you receive birth-control counseling, it turns out that the pregnant women received the birth-control counseling from the doctor in 56 percent in the pregnant group and in 65 in the non-pregnant group. Consequently, 30 percent received that birth-control counseling from another healthcare provider compared to 20 percent in the non-pregnant group.

[Slide.]

This survey is followed by the monthly comprehension questions. The patient must complete the comprehension questions correctly and this is a condition to proceed to receiving an RMA. The questions are randomly selected from a repository of set questions but they are tailored to the patient's choices made earlier in regards to the contraception methods.

The questions are really broken down into six categories, general iPLEDGE Program steps, general contraception requirements, birth defects and pregnancy, safety information about not sharing the drug and not donating blood, filling a prescription and contraception questions.

The way this works, the woman is presented with one question for each category. If her response is correct, she carries on to the next question in the next category. If the response is incorrect, she is faced with a second question for the same category.

If that question is, again, answered

incorrectly, she fails this comprehension test.

[Slide.]

Let's look at how the performance was reflected in the data. You are already familiar with this format comparing the non-pregnant with the pregnant group. The vast majority of all females actually passed the comprehension test on the first attempt, 83 percent for the non-pregnant, which is a very large group, and 79.4 percent of the pregnant women. There is really no difference in this regard.

A small number of women in both groups managed to pass the comprehension test after one failed attempt, 12.4 percent in the non-pregnant and 18.8 percent among the pregnant group.

Just to highlight, there really is no apparent difference between these groups when we look at these parameters.

[Slide.]

It is very important to look at the selection of contraception methods that the women made all along this year. During the office visit,

the prescriber and the patient determined the appropriate methods of contraception for herself. The prescriber enters the selected contraception choice for this patient into the iPLEDGE system.

Now, the patient enters her two chosen methods of contraception into the system independently. However, the primary method entered by the prescriber and by the patient must match in order for that female of child-bearing potential to continue in the process.

[Slide.]

Here is a detailed description of the methods of contraception, the combinations that were selected. Here is the program of all females of child-bearing potential. Again, the number here reflects the total number that have made their choices and entered into the system. This is not the number of the women that actually received at least one RMA. Here is the small pregnant group.

42 percent of the time, the female of child-bearing potential indicated that their choice was the combination of birth-control pills and male

condoms. This choice in the pregnant group was selected 72 percent of time.

The second method if contraception here was abstinence selected 43 percent of the time by all females of child-bearing potential and, among the pregnant group, this method of contraception was selected 18 percent of the time. Then there are smaller percentages for a host of other combinations.

[Slide.]

In summary, I would like to point out to you that the iPLEDGE Program is an integrated program supporting the defined public-health goals. The proposed program changes are intended to enhance the flexibility, to reduce interruption of treatment and to actually reduce the stakeholder burden.

The Year 1 iPLEDGE, as described, provides a baseline information, as indicated earlier, at the Time 0 picture. No identifiable difference between pregnant or non-pregnant females of child-bearing potential could be highlighted based

on the data that we have shared with you this morning.

The educational messages are reaching the patients and, at the end of the day, individual patient behavior plays a key role in the program outcome despite very intense educational efforts.

Thank you.

DR. BIGBY: I would like to now recognize Dr. Kornegay who is going to discuss perspectives on pregnancy, registry and patient knowledge assessment.

Perspectives on Pregnant Registry and Patient Knowledge Assessment

MS. KORNEGAY: Good morning.

[Slide.]

My talk today is going to describe some of the early challenges in evaluating the iPLEDGE Program. I will focus on issues that will affect the evaluation of the overall program effectiveness rather than one specific area.

[Slide.]

I will address challenges in two areas,

the pregnant registry and root-cause analysis and the knowledge and behavior assessment. For both of these topics, I will talk about their role in iPLEDGE, describe possible barriers that may be limiting their effectiveness as implemented in the first year, and suggest solutions that could be used to address these emerging issues.

I will also discuss the role of a comparison group in evaluating iPLEDGE. Finally, I will present a summary of these preliminary observations.

[Slide.]

The first challenges that I will discuss are related to the pregnancy registry and root-cause analysis.

[Slide.]

The root-cause analysis, or RCA, was initially proposed at the Drug Safety and Risk Management and Dermatologic and Ophthalmic Drugs Joint Advisory Committee in February of 2004. The purpose of this tool is to gather information from women who become pregnant with on isotretinoin in

order to determine whether the Risk Management Program has been less than effective.

The RCA helps to identify possible ways to strengthen the program to address the problem. The RCA was implemented as part of pregnant registry in the iPLEDGE Program.

[Slide.]

All women who report a pregnancy are included in the pregnancy registry and followed up. The RCA is a part of the larger registry process and is completed after the registry informed consent and initial registry information is obtained. The intent is for the RCA to be done for all women in the registry.

[Slide.]

The sponsors submit reports every quarter to provide information about the iPLEDGE Program and pregnancies that have occurred. In the first year of iPLEDGE, approximately 10 percent of pregnant patients that definitely were exposed or that may have been exposed to isotretinoin participated in the RCA.

The participation level is too low to enable the information to be used in aggregate to approve the iPLEDGE Program.

[Slide.]

Although specific factors contributing to the low RCA participation rate are not known, the following are some issues that may be potential barriers for patient participation.

There is a significant time element involved in participation in the RCA. After the initial report, information is collected from both the patient and their pregnancy healthcare provider every quarter until the end of the pregnancy or until the infant is one year old.

The registry involves an additional informed consent and the RCA and registry follow-up questionnaires are generally several pages long. Of necessity, both the RCA and registry ask for sensitive information and can be intrusive.

[Slide.]

Once the woman finds out she is pregnant, she may not have any further contact with the

isotretinoin prescriber so she could be lost-to-follow-up. Neither the regulatory nor the RCA is widely promoted and patients and providers may not understand why their participation is important.

The RCA's administered only after the patient agrees to participate in the registry and information on the patient's medical and pregnancy history has been collected. Although the intent is for the RCA to be given to all women in the registry, after implementation, it was discovered that only a small number of registry participants were completing the RCA form.

[Slide.]

The goal of the RCA is to provide feedback on potential gaps in iPLEDGE. To achieve this, it is necessary to have adequate participation levels in the group of women who became pregnant while on isotretinoin.

These are some ideas that may help increase awareness and involvement in this part of iPLEDGE; simplify the informed-consent process and

questionnaires while remaining focused on the goal of improving iPLEDGE, continue to ensure that interviewers present the questions in a non-judgmental manner, publicize the existence and purpose of the registry and RCA, collect RCA information as soon as possible after the pregnancy is reported.

In response to the participation levels seen after implementation, sponsors have altered the data-gathering process so that the RCA information is now collected when the pregnancy is initially reported. However, some of these other ideas listed should also be considered.

[Slide.]

Next, I would like to address some emerging concerns in the knowledge and behavior assessment in iPLEDGE.

Patient education is a central tenet of the iPLEDGE Program. All patients who wish to take isotretinoin are given brochures and workbooks that discuss the unique risks and patient responsibilities that are required to take the drug

responsibly.

Because of the drug's teratogenicity, females of child-bearing potential are given additional materials that outline special risks that they should be aware of and precautions that they must take to avoid pregnancy while exposed to isotretinoin. Samples of the educational materials were distributed to you earlier.

[Slide.]

In addition to the extensive educational materials, iPLEDGE makes an effort to provide contraceptive counseling for all patients, particularly females of child-bearing potential.

Prior to prescribing isotretinoin, healthcare providers are required to provide contraceptive counseling. If the provider is unable or does not wish to provide counseling, he or she can refer the patient to a contraception counselor. The iPLEDGE Program will cover the cost of this initial counseling if requested.

[Slide.]

Females of child-bearing potential are

required to answer a series of questions pertaining to the safe use of isotretinoin every month of therapy. Questions at the start of therapy ensure that patients have received and read the iPLEDGE educational materials. These questions are only asked the first month a patient is taking isotretinoin.

Questions during therapy are intended to measure patient knowledge and comprehension of key messages of iPLEDGE. They also serve to reinforce important safety concepts. These questions must be answered correctly every month prior to receiving their prescription.

[Slide.]

In an effort to educate patients about this drug, there are a number of materials to be reviewed prior to the first dose. Women of child-bearing potential, in particular, receive over 50 pages of material at the start of therapy. The patient may experience information overload.

There is research that suggests that more information is not always better. In a recent

study of the educational materials associated with isotretinoin, patients who read the materials were not able to answer a series of questions about therapy any better than if they had guessed all of the answers.

Second, there appears to be some inconsistency between the additional informed-consent document signed by females of child-bearing potential and what they report during the initial monthly questions.

Although the informed-consent document that females of child-bearing potential sign at the beginning of therapy states that a woman has been counseled by the healthcare provider or on the contraceptive requirements of isotretinoin therapy and why they are important, 13 percent of women subsequently reported that they had not received contraceptive counseling at the start of therapy.

[Slide.]

There is the possibility that the messages in the educational materials are not being understood by females of child-bearing potential.

Patient's questions at the start of therapy consistently indicate that over 95 percent of women have received and read the isotretinoin materials.

However, 38 percent of women answered the following true/false question incorrectly; you can use any forms of birth control for iPLEDGE. The correct answer is, false.

[Slide.]

Finally, some of the monthly questions may not be worded clearly enough for patients who demonstrate appropriate knowledge of the iPLEDGE Program.

To illustrate, I have a question that was asked during the first year of the iPLEDGE Program Depending on the type of birth-control method chosen, between 21 and 62 percent of women answered this question incorrectly.

Sohail, could you go to Slide 32, please.

[Slide.]

This question is from the monthly questions used in the first year of iPLEDGE. A similar question is asked for all forms of birth

control chosen by the participant. The question states, "I have been using an IUD for three years and I have not gotten pregnant. Why do I need another form of birth control now?"

The possible answers are; any form of birth control can fail, the IUD does not protect against sexually transmitted diseases, the IUD is not an acceptable form of birth control in the iPLEDGE Program, or all of the above.

The correct answer is the first one, all of the above--or; I'm sorry--the first one, any form of birth control can fail. However, since the first two responses are true, it is not hard to see how a patient could pick the incorrect answer but still understand the basic message that two effective forms of birth control are necessary while she is exposed to isotretinoin.

31 percent of respondents answered this particular question incorrectly.

Can you go back to Slide 17.

[Slide, continued.]

Of note, this question has been changed as

part of the supplement that is being discussed today. The questions and answers are now clearer and should be easier to understand.

[Slide.]

While the educational component of the program is very large and complex, there may be some actions that can be taken to ensure that the basic messages of iPLEDGE continue to be communicated effectively. The patient education materials should not be any longer than necessary and should be focused on helping women understand the essentials of the iPLEDGE Program.

The language and the materials should be clear, consistent and understandable by the general public. Changes to the educational materials should be tested prior to distribution as part of the iPLEDGE Program.

[Slide.]

Although many women of child-bearing potential may receive contraception from another healthcare provider, isotretinoin prescribers still need to review iPLEDGE's additional requirements.

The need for two effective forms of birth control during exposure to isotretinoin should be emphasized.

The monthly questions should continue to be examined to assure that they remain focused on assessing knowledge of iPLEDGE. They should be clear and correct answers should directly relate to important iPLEDGE concepts. The questions should be designed to provide an accurate measure of a patient's knowledge.

[Slide.]

An appropriate comparison group to the patients that become pregnant is very important in putting the results of the pregnancy registry, RCA and the knowledge questions in context and using this information to improve iPLEDGE.

[Slide.]

The RCA collects data on actual contraception use from women who become pregnant. Comparable information is not available from the women who did not get pregnant. Having the ability to make this comparison will help place the RCA

information on behavior and contraceptive practices in context.

[Slide.]

The Agency and the sponsor should consider how this missing piece of information could best be obtained. For example, a short survey could be done in a random sample of non-pregnant females. Given the comprehensive nature of the iPLEDGE Program, it will be important to make such a study minimally intrusive.

Having these results will improve the quality of the evaluation of iPLEDGE by helping to provide direction on possible areas of enhancements for the program.

[Slide.]

Finally, I would like to summarize our observations on the pregnancy registry and patient knowledge components after the first year of experience with iPLEDGE.

[Slide.]

The Agency is very interested in increasing the RCA participation rate. As one of

the primary evaluation vehicles for iPLEDGE, it is important that sufficient information be available for future analyses. We would like to ensure that females of child-bearing potential, in particular, have a good understanding of the risks and responsibilities associated with isotretinoin therapy.

In conjunction with that, we would like to ensure that the assessment of the patient's knowledge is valid and measures the understanding accurately. Some minor program adjustments in the upcoming period may help in achieving these goals but it is of overriding concern not to unduly or unnecessarily disrupt the iPLEDGE Program.

[Slide.]

We would also like to emphasize that the goal of the evaluation is to ascertain if there are parts of iPLEDGE that can be enhance to improve its overall effectiveness.

While iPLEDGE strives to minimize the number of pregnancies exposed to isotretinoin, any form of contraception can fail even with perfect

use. Therefore, the program may never be able to prevent all fetal exposures.

Additionally, iPLEDGE, like any other RiskMAP may be limited in its ability to effect behavior change.

Thank you for your attention.

Clarifying Questions and Answers

DR. BIGBY: At this point, I think we can ask of the presenters qualifying questions. I would like to remind the committee that the questions that we have been asked to address are the following.

The changes proposed in the pending supplement are intended to increase program flexibility and to reduce interruptions of treatment. Please discuss whether the proposed changes are acceptable.

The second one is, discuss approaches to enhancing voluntary participation in the pregnancy registry within the iPLEDGE Program.

The final is, are there additional recommendations for the future to enhance the

risk-management functions of the iPLEDGE Program.

So, with those questions in mind, Dr. Mitchell?

DR. MITCHELL: I will try to confine my initial questions to some clarifying questions just in terms of methods. The critical elements of the evaluation, obviously, relate to identifying women who have completed their course of therapy so that follow-up information can be gathered, number one.

Number two, is the RCA, which we have heard has either a 10 percent or an 18 percent participation rate, depending on which speaker presented it.

But could the sponsor describe what the triggers are to the follow-up process. We are told that a patient who completes therapy is then expected to have two pregnancy tests. But how is completion of therapy identified and how is the follow-up process made rigorous. That is my first question.

The second question is could--the key elements of the RCA participation rates have to do,

undoubtedly, with the way this is approached to patients, and could the sponsor describe how that approach is made. By whom? Are these trained interviewers? Are they one of a thousand different potential interviewers who may be getting that call?

So, if the sponsor could provide some detail on those two process questions, it would be very helpful.

MR. SHAMP: Jim Shamp, Covance. I believe your first question was the triggers for the follow up at the end of therapy; is that correct?

DR. MITCHELL: Yes.

MR. SHAMP: There are two triggers that indicate the end of therapy. Every month when the prescriber enters the counseling confirmation in the system, there is a checkbox there to indicate that this is the patient's last month of therapy. So that is one of the triggers.

Additionally, if the system recognizes a lack of activity on that patient, we also change the status of that patient to indicate that there

has been a lack of activity and we should look at that patient.

DR. MITCHELL: Thank you. So, when there is a lack of activity--so let's say a month goes by, two months go by, there is some defined interval where there is no new prescription being written; is that correct?

MR. SHAMP: The activity in the system is specifically looking for the confirmation from the prescriber confirming that in the system. That is the beginning of the process for the prescription.

DR. MITCHELL: So, at what point does that take place? In other words, the system is screening for activity but I am not hearing you about--is this a month of no activity, two months of no activity? At what point?

MR. SHAMP: It is normal for a month of non-activity to go by because of a 30-day prescription. So I believe the window is actually at 53 days. So it is a month plus a little bit.

DR. MITCHELL: The 23 days. And then what happens at that point?

MR. SHAMP: At that point, we do have a process where we do attempt contacting the prescriber. We try two phone calls followed by a letter the prescriber. If that is not successful, we then have two phone-call attempts to the patient followed by a letter to the patient.

DR. MITCHELL: On the RCA, if someone could just answer that.

DR. PLATT: So, could we just follow up the last discussion? Of the 97,000 or so women who have been dispensed one of these drugs, what faction have discontinued and what proportion of those have had the two pregnant test follow ups on exit?

MR. SHAMP: We have not completed the analysis on that and we do not have that data available today.

DR. BIGBY: So did you get the second part of your question answered?

DR. MITCHELL: No.

DR. BIGBY: So does somebody want to address the second part of the question?

DR. RESHEF: Dan Reshef from Roche. The RCA form and the RCA analysis really rely primarily and foremost, as we all understand, on private sensitive information that the patient must be willing to share with the program, with the interviewer.

It is true, as you have seen, that the RCA rate, if you will, in Year 1, was roughly 10 percent. But there are detailed follow-up procedures and there are genuine attempts to enhance et quality of the RCA form.

This entails a number of telephone contact attempts. Those are followed by a traceable letter to the prescriber to the patient and only after that the patient is deemed lost-to-follow-up.

But I would like to share with you some additional information that is truly preliminary, is outside of Year 1, but is interesting because it reflects what we know in the last four months.

Could I please have the slide up?

[Slide.]

What you can see on this table is the most

recent information that reflects the month of March, April, May and June of this year outside of the numbers that were presented earlier. I would like to point out to you that, in fact, if you please look at the last line on this side, the number of RCA forms completed actually has gone up and we think it reflects the most recent changes in the procedure and our approach to obtaining the RCA.

You can see that now, albeit small numbers, but in these four months, we are above 30 percent in obtaining the RCAs and we think that this is an initial indication that is positive.

The next question will be Dr. Crawford.

DR. CRAWFORD: Thank you, Mr. Chairman. May I ask three questions, two of which are pretty quick, one which might be a little deeper.

The first one, Mr. Shamp, would you please come back. You showed us data on your Slides 14 and 15 with respect to the program iPLEDGE being offered for those whose languages predominantly are English and Spanish.

I do recall, in 2004, some of the sponsors had programs that were available in many other languages. So my big question is are those who do not speak English or Spanish denied access to participate in iPLEDGE and, even if they do speak and can comprehend this, is there a help line available for those who might need help in languages beyond those two?

MR. SHAMP: Jim Shamp, Covance. We do not believe that these patients that do not speak English and Spanish are being denied. Through the call center, there is a language line available for any translation that is required.

DR. CRAWFORD: Thank you. The second quick question, Dr. Diglisic showed us in her slides, I believe it was 20 and 21, 2-year prescription data on the isotretinoin prescription dispensed. In your presentation, Mr. Shamp, you also told us about those prescriptions that were denied.

Since one of the issues before this committee will be regarding the 23-day lockout

period, I want to know is there any way to put those figures together, how many prescriptions are denied because it is within that 23-day lockout period.

MR. SHAMP: Jim Shamp, Covance. It is possible to put those numbers together. We don't have those numbers with us today. But, as you saw, certainly for the males and females of non-child-bearing potential, waiting until after their window has expired is the second-most common. I don't recall if it was one of the other reasons for the females of child-bearing potential, but the data can be determined. So, yes.

DR. CRAWFORD: This is my last question, the deeper one, which I address to any of the sponsors or the agency who might wish to respond. My biggest concern about what we have been presented today--certainly, it is a huge amount of data from the iPLEDGE Program, but I must have questions in my mind about the data that are not presented because, one, I still have some concerns because the numbers aren't available for those who

might not understand the language or are, perhaps, skirting the system or for the men who may or may not be sharing prescriptions.

Do we have any data to present on pregnancy exposures for women who are not participants in iPLEDGE because, surely, that data might be available and can be compiled from certain sources.

Thank you.

DR. BIGBY: Does anybody have knowledge about pregnancies of women not participating in the iPLEDGE Program?

DR. KARWOSKI: Claudia Karwoski, OSC. We are not aware of any data right now of patients having received this, being pregnant outside of the iPLEDGE Program.

DR. BIGBY: The next one is Dr. Gross.

DR. RESHEF: Dan Reshef from Roche. The isotretinoin pregnancy registry is meant to capture any pregnancy being reported and, in fact, in the registry, we have 122 pregnancies that are true iPLEDGE pregnancies as described by the slide that

I have shared with you earlier.

But there are a number of additional pregnancies that have been captured in the registry. There is a total of 19 non-registered patients that reported a pregnancy to the registry. And there is an additional number of reports that came in from women that participated one way or another in previous earlier programs.

DR. GROSS: I have three comments and questions. Is there any reason that participation in the registry and a root-cause analysis couldn't be agreed upon for females at initial induction into the program rather than waiting for the time of pregnancy?

I will just give that question now. Then I have two others.

DR. RESHEF: Dan Reshef from Roche. I think that it is very clear to prescribers and to all stakeholders including the patients that, via the education sessions and via the two signed informed consents, there is an agreement, if you will, to participate in the registry and to provide

information via the root-cause analysis form.

But this happens at an early stage when the patient is motivated and interested in the treatment. Later on, when she becomes pregnant, as pointed out by the speaker from the FDA, that motivation may change and, in fact, some of these women may not be traceable or may not be willing to share that information, contrary to their original commitment.

DR. GROSS: My next question is is data available on prescribers' patients and/or pregnancy from the earlier risk-management programs such as SMART or APPP or is that only available under the iPLEDGE Program because it would be nice to see how the increasing restrictive risk-management programs reduced the occurrence of pregnancy relative to the total numbers give the drug.

DR. RESHEF: Dan Reshef from Roche. It was pointed out by speakers from the FDA that these attempts at comparing numbers of pregnancies captured in iPLEDGE with the number of pregnancies captured in earlier RiskMAPs is very difficult and

may be attempted but, at best, just look at the numbers.

I would like to provide you with the numbers. Slide up, please.

[Slide.]

What you see here, without an attempt to compare, is a description of the total number of pregnancies captured in each year of the SMART program. The total number here, in Year 1, was 224 moving to 229, 190 and 123.

Again, it is very difficult to compare because there is no denominator here. These are completely voluntary reports and, in fact, these reported numbers may be farther away from reality, from the real numbers, of pregnancy.

In iPLEDGE, because of the closed nature of the program, because of the nature of the program being mandatory, the number--we believe that the number of pregnancies captured is probably much closer to reality. But that is as far as I could go.

DR. GROSS: Thank you. The last issue, a