small but maybe not so small issue, is what is the definition of a female of non-childbearing potential since women are becoming pregnant at older ages today.

DR. RESHEF: Dan Reshef from Roche. Slide up.

[Slide.]

What you can see on the screen is the actual definition agreed by all participants and the agency in the program. The definition of a female of child-bearing potential is a non-menopausal female who has not had a hysterectomy, bilateral oophorectomy or medically documented ovarian failure. This includes a young woman who has not yet started menstruating.

A woman who has had a tubal sterilization is considered a female patient of child-bearing potential in the iPLEDGE Program.

DR. BIGBY: Can I just ask a quick clarifying question about one of the questions you just answered. In that slide you showed of numbers of pregnancies during the SMART program, do you

have denominators, like do you have the registered women of child-bearing-potential numbers as a denominator, given that I do understand that both the accuracy of the numerator and denominator are suspect?

DR. RESHEF: As we all know, there was no registration step in the SMART, in the previous RiskMAP program, so it is very difficult to almost guess such a denominator. However, there were some estimates as to patient exposure to isotretinoin and that is really as far as we could go.

Could I have the slide up, please.

[Slide.]

This is a slide that presents estimates that were made at the time by year in terms of males and females. You can see the numbers. I don't think that these are true denominators.

DR. BIGBY: The next questioner is Dr. Hennessy.

DR. HENNESSY: Thank you. I have three quick questions. One, girls who are not yet menstruating will start menstruating at some point

and I am wondering how they get shifted from being of not of child-bearing potential to child-bearing potential in the system.

Two, I am wondering why the 90 pregnancies outside of the iPLEDGE Program are not regarded as a major failure of the system.

Three, the whole reason for doing this is to reduce birth defects. We haven't heard anything about the outcomes of the pregnancies.

DR. RESHEF: Dan Reshef from Roche. You are absolutely correct. A girl that is not menstruating may begin at some point. They all begin at some point. But we rely here primarily on the medical practitioner that is the person that actually interacts directly with every single patient. The sponsors do not interact in any way with the patient.

The determination whether this particular female patient is of child-bearing potential or, if not, relies at any point in time with the physician that interacts with the patient.

I believe your second--can you please

repeat your second question.

DR. HENNESSY: I understood that there were 90 pregnancies that were reported outside of the iPLEDGE system and, if that is true, why that doesn't represent a major failure of the iPLEDGE system.

DR. RESHEF: I am afraid that the number was incorrect. The number of these pregnancies was 19, not 90. 19--1,9. Bring the slide up, please.

[Slide.]

DR. RESHEF: Here is a further detail of these 19 pregnancies where the source of exposure was non-iPLEDGE. Two such pregnancies obtained the drug from outside the U.S. Two pregnancies obtained the drug from a pharmacy that we don't know. One patient took, accidentally, isotretinoin once instead of--because of a mistake. She thought she was taking ibuprofen. This happened, I believe, in relation to a child that was taking the drug for an off-label indication. One patient took the mother's prescription. For 13 of those, we do not really know.

DR. BIGBY: The next questioner is Dr. Thiers.

DR. HENNESSY: I'm sorry. I had asked about pregnancy outcomes and didn't hear an answer on that.

DR. RESHEF: Correct. We are very open to share the pregnancy outcomes. Of the 122 pregnancies, some pregnancies were terminated, either electively or therapeutically. We are aware of one live birth with a normal outcome. A number of pregnancies, because it is dynamic data as we all understand, the number of pregnancies were still ongoing when we took that snapshot and, for a number of pregnancies, we actually do not have the information. It never came back in terms of outcomes.

DR. HENNESSY: Can I follow up on that? So, one, this is just verbal. There is not a slide on this which makes me a little bit concerned. Too, I heard nothing about any pregnancies that resulted in any birth defects. Is that what I understand?

DR. RESHEF: Correct.

[Slide.]

I put on the screen--I have to share with you the numbers. 54 of the 122 were an elective termination of the pregnancy . A spontaneous abortion occurred in 17 instances. As I pointed out, one live birth with a normal outcome. 15 pregnancies were still continuing as of June 25. And for 35 of the 122, we do not have the information regarding the outcome.

As to the birth defects, none of the sponsors is aware to date of any single birth defect reported in this year.

DR. HENNESSY: That number of 35 unknown is very, very concerning.

DR. BIGBY: Dr. Thiers.

DR. THIERS: Thank you. In the spirit of equality, I will also ask three very short questions. This is my first meeting so I apologize if any of these issues have been addressed previously.

Before isotretinoin, the great feared

teratogen was thalidomide which, as you all know, is back on the market. It looks to me, from the data that we have seen today, that the pregnancy rate of females of child-bearing potential with iPLEDGE is about a tenth of a percent.

Does anybody have any data what the equivalent data is from the STEPS Program which is incredibly simple compared to iPLEDGE. Is STEPS inferior in terms of preventing pregnancy, superior, equal or do we not have the data? I will ask anybody who knows the answer to respond.

DR. KARWOSKI: Claudia Karwoski, OSC. I guess, with regard to the programs, the iPLEDGE Program is actually more rigorous in terms of requiring the documentation of a negative pregnancy test, the actual results of the test. And it requires to pregnancy tests prior to initiating therapy in comparison to STEPS which only requires the initial baseline pregnancy test and the monthly pregnancy testing

We are aware of one exposed pregnancy to thalidomide. There had been positive pregnancies

that have occurred that were false positives because beta HCG is often elevated in these tests. When they went back and followed up, these turned out to be false positive tests. So we are aware of one positive exposure. In this particular case, I believe the patient had a spontaneous abortion.

As far as the denominator used, I don't actually have those numbers. It is far less than what--well, what the use is for isotretinoin and the exposure in females of child-bearing potential is much less, somewhere in the neighborhood of, let's say, 3 to 7 percent. I don't have those actual figures.

DR. THIERS: Obviously, what I am getting at is I don't necessarily believe that more is better. Again, STEPS is incredibly easy to navigate. I am just wondering if that is as effective as iPLEDGE. But I guess we don't have any way of comparing them.

DR. MITCHELL: If I could respond, having been involved in evaluations both of isotretinoin's risk-management program and STEPS, we keep pointing

out and people keep failing to hear it, unfortunately, the populations being treated with these drugs are about as different as any populations--

DR. THIERS: Right. That is why I am just suggesting--

DR. MITCHELL: Just females of child-bearing potential. But females of child-bearing potential typically have multiple myeloma. They are not young, healthy women. So I think--I could debate about whether we can make comparisons between iPLEDGE before and after. I think to make comparisons between those two drugs and those programs is really not going to be productive because those are simply not women who are healthy.

DR. THIERS: Okay. The second question is, again, this may have been covered at a previous meeting. Is the idea of men sharing their prescription with women--is that based on a theoretical concern or did we know that that happens? Is that why they were included? What is

the basis of including men in this? Was this a common problem?

DR. KWEDER: I can address that. Sandra Kweder. And Allen may be able to address it as well. We know that, particularly among young people, adolescents, teenagers, prescription sharing is a common phenomenon. As you saw from one of those reports, one patient took her mother's prescription, one of the ones who became pregnant.

The importance of not sharing prescriptions is really a key message. So you can't just limit that message to females of child-bearing potential.

DR. THIERS: Okay. The last question, which I think should be easy to answer, this is obviously a very comprehensive program. There are some intangible costs which are, for example, the time involved. There are tangible costs like whatever Covance is being paid, the technology cost.

I have got enough of these in my office to populate a national forest. I was just curious.

What has been the cost of the iPLEDGE Program in its first year since its inception? Does anybody have any idea?

MR. GREWAL: Good morning. Mankaran Grewal from Ranbaxy. The cost of the iPLEDGE Program over the first three years that we have--that we are working on is about $100 million.

DR. BIGBY: We are going to take one more question and then we are going to have a break. I should remind you that these are sort of qualifying questions. We will have time at the end to sort of discuss the issues more thoroughly.

Dr. Kresel.

DR. KRESEL: Thank you. I was wondering if there is any data as to how long the patients had been taking isotretinoin before they became pregnant. We see data that says, when they became pregnant in terms of before, during or after therapy. But I wonder if there is any relationship, in terms of they get pregnant on their third month or fourth month and so there is some kind of relationship between just being tired

of following the directions.

They start out in the first month and abstinence is their form of birth control. And they thought they could do that, but, by the third month, they are not longer abstinent.

MR. SHAMP: Jim Shamp, Covance. That is data that we can certainly get but we do not have that with us today. What we did have today, I believe, was discussed earlier with the breakdown of when, before, during or after therapy.

DR. BIGBY: So we are going to take a break now. We will reconvene promptly at 10:15.

[Break.]

DR. BIGBY: We are going to start the open public hearing.

**Open Public Hearing**

DR. BIGBY: Both the Food and Drug 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, FDA believes that it is important to understand the

context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the Open Public Hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this Open Public Hearing to be conducted in a fair, open way where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

The floor is open to the first speaker.

DR. BAKER: Good morning. My name is Diane Baker. I am a practicing dermatologist from Portland, Oregon and currently serve as the President of the American Academy of Dermatology. I am here today representing on behalf of the 15,000 members of the Academy. I have no conflicts of interest to declare.

I appreciate this opportunity to share with you the dermatology community's strong commitment to prevent fetal exposure to isotretinoin. I assure you that dermatologists are absolutely committed to this goal of iPLEDGE. The

health, safety and well-being of all our patients taking this medication is of paramount importance to us.

Although we have learned today that the goal of zero fetal exposure to isotretinoin has not been achieved in the first year of iPLEDGE, we have also learned that educational messages about the need to avoid pregnancy during isotretinoin therapy and one month before and after, are being communicated by prescribers and are reaching female patients.

This first year's worth of reporting provides a baseline count of pregnancy. As the program matures, and aided by improvements in the program and pregnancy root-cause analyses, prescribers and patients will learn how to reduce the number of pregnancies.

The first-year results should not prevent the proposed changes outlined in the briefing documents from being implemented. We remain strongly committed to improvements in the iPLEDGE Program that will help it achieve its primary goal.

However, certain elements of the iPLEDGE Program do not serve its primary goal of preventing fetal exposure. I refer to the 23-day lockout period currently in place for women of child-bearing potential who do not pick up their prescriptions within 7 days of the office visit.

We are pleased to note that removal of this element, which can actually undermine the safe and effective use of this uniquely valuable medication, is one of the proposed revision to the iPLEDGE Program presented here today. We fully support this revision because the current lockout period leads to interruptions in treatment and results in prolongation of the period of time that patients are exposed to isotretinoin and, if everything else is the same, the risk of fetal exposure is directly related to the total exposure to isotretinoin.

In addition to removing a restriction that prolongs exposure to isotretinoin and interrupts therapy, the elimination of the lockout period allows for a new prescription to be issued and

filled when needed before a patient's next office visit. This is essential for the safe and effective use of isotretinoin which often does require both dosage adjustments.

We also fully support the other proposed iPLEDGE Program changes including linkage of the start of the 7-day prescription window to the date of pregnancy testing rather than the date of office visit and extension of prescription windows for males and females of non-childbearing potential.

We also support the changes proposed to facilitate interactions with the iPLEDGE system as listed in Appendix 4 of the briefing document.

Initially, patients and their prescribing physicians did experience frustrating delays in initiating and continuing therapy with isotretinoin--for instance, inordinately long wait times at the iPLEDGE Call Center and difficulties with on-line procedures. Today, nearly 18 months later, the call center's has improved and callers are usually able to obtain help within a few minutes.

Improvements in call center performance and streamlining of case management were changes asked for by dermatologists in an August, 2006 iPLEDGE survey commissioned by the American Academy of Dermatology. Some iPLEDGE elements were modified to serve the goal of iPLEDGE eliminating fetal risk.

We are committed to working with all stakeholders to make iPLEDGE more successful by eliminating or modifying elements that interfere with the safe and effective use of isotretinoin.

We also urge the FDA and the program sponsors to reaffirm their commitment to confidentiality of patient information. An Academy member recently contacted our Washington office to report that a patient was trial lawyer asking if the patient had experienced any adverse health effects while taking isotretinoin.

It is alarming that a third party apparently gained access to sensitive patient information. RiskMAPs such as iPLEDGE must ensure the confidentiality of patient data and guarantee

that it is not available to third-parties.

Another situation that needs to be addressed is the incompatibility of iPLEDGE with some widely used web applications. We have heard from members, specifically Mac users, about incompatibilities that made Internet contact for them impossible.

Lastly, we make a plea for the reinstatement of programs by the manufacturers to provide isotretinoin free of charge to low-income or indigent patients. This assistance program was discontinued under iPLEDGE. The Academy urges the sponsors to restart this program to ensure that this uniquely valuable medication is available to all qualified patients who need isotretinoin.

Since it became available for the treatment of severe acne in 1983, isotretinoin has saved multitudes of patients from the suffering associated with severe acne and the lifelong scars, both psychological and physical, that accompany this disease.

Before isotretinoin became available,

there was no effective treatment for those afflicted with the disease depicted here and no way to prevent this type of scarring. Treatment with isotretinoin can prevent this.

As Congress prepares to vote on an FDA reform bill that will possibly lead to more iPLEDGE-style programs to manage risks linked to some drugs, it is important to apply what we have learned form iPLEDGE. We have learned that closed distribution risk-management programs such as iPLEDGE must ensure patient confidentiality.

These programs must also be user-friendly, workable and streamlined so that the safe and effective use of valuable medication is not compromised.

Despite the challenges, it is possible to make risk-management programs more workable and to better achieve their goals. The Academy is committed, on behalf of our patients, to the goal of iPLEDGE, eliminating fetal risk. And we are equally committed, on behalf of our patients, to continued access to this uniquely valuable

treatment for our patients with severe life-altering skin disease.

Thank you for your attention to the Academy's views and for considering our suggestions for iPLEDGE improvements.

DR. BIGBY: Thank you. The Chair recognizes the second public speaker.

MR. GELLMAN: Thank you. My name is Robert Gellman. I am a privacy consultant here in Washington and I am appearing here today on behalf of the World Privacy Forum. Pam Dixon is the Executive Director of the Forum and could not appear here today on short notice. We have no conflicts to report.

The World Privacy Forum is a nonprofit, public-interest group, that specializes in privacy issues and, in particular, health privacy issues. Last year, a World Privacy Foundation report first identified and defined medical identity theft as a significant healthcare and privacy problem.

I have two simple messages today. First, the iPLEDGE Program has inadequate privacy

protections. Second, the FDA does not require RiskMAP programs, of which iPLEDGE is one, to meet any privacy standard. As a result, the iPLEDGE Program has a privacy policy that allows Covance to use and disclose personal information for marketing purposes with the consent of the patient.

The policy is so unrestricted that it appears to allow disclosure to junk mailers, telemarketers, banks, data brokers and others. The World Privacy Forum believes that patient information should not be a profit center for Covance or for any of the participating pharmaceutical manufacturers.

Covance stated in an e-mail that it sent last week to Pam Dixon that it would not use iPLEDGE information for marketing purposes. This statement is most welcome. The World Privacy Forum will wait to see the precise scope of that commitment, how it is implemented and how physicians are informed of the new policy as well as patients.

A privacy policy needs to be more than a

prohibition against marketing uses of patient information. It should address all elements of fair information practices, including notice, access and correction, use and disclosure limits, security, accountability and the other elements, all of which, by the way, are reflected in the HIPAA Privacy Rule.

The broader issue here is the failure of the FDA to set privacy requirements for RiskMAP activities. The FDA did not address privacy and that allowed Covance to issue its original policy allowing marketing use. It appears that the FDA does not think that HIPAA applies to RiskMAP programs. We do not agree that HIPAA is necessarily inapplicable here, but there are questions.

If it is the position of the FDA and the industry that HIPAA does not apply, then patients need to be told this quite expressly. And we also believe that FDA should act to fill this glaring loophole.

I thank you and I would be happy to answer

any questions that you have.

DR. BIGBY: Thank you very much. The Chair recognizes the third speaker.

MS. BARTON: My name is Michelle Barton. I am a nurse practitioner, dermatology nurse practitioner. I practice in Southern Maryland and I am here today as a representative for the Dermatology Nurses Association.

I have been a registered nurse for 20-something years. I have been in practice as nurse practitioner for 11 and in the dermatology specialty for over seven. I have no conflict of interest.

I would first like to address the iPLEDGE Program patient benefits but which still remain a concern for us. Some of the problems continue to be; difficulty accessing the program, especially long waits on hold or difficulty communicating between departments. Some of those assistants in the iPLEDGE Program don't have access to the prompt computer screen and, for that reason, haven't been able to answer questions and this results in long

delays in therapy.

There have also been some concerns about our patients that are unable to afford the medication or have no medical insurance and, because of that lack of indigent program that the medication is not available to them.

Many providers also relate concerns with their own staff's ability to comprehend the material because many of them are medical assistants. They are not registered nurses or LPNs. Because of this, the process becomes even more labor-intensive as the material is difficult for the staff to comprehend and also pass that information on to the patient.

In my own practice, we have tried instituting a log and an intake sheet which also has review of systems and a past medical history but all those forms add to a cumbersome file.

The other second problem that we want to address is the discontinuation of the 23-day lockout period for females of child-bearing potential. The problem for us has been that, if

they don't pick up that prescription within a 7-day window, then they are locked out until the next available date.

Some of the examples where this has been a real problem has been, in one instance, there was a female patient whose prescription was written for 60 pills. It should have been 90. Unfortunately, the provider, the patient and neither the pharmacy noticed the discrepancy until the prescription was filled.

She called the next day and, unfortunately, because the prescription was already filled, there was nothing that could be done and her dose was reduced for that month meaning that her exposure to the medication was prolonged.

Another example that we have had problems with is the pharmacies may not carry isotretinoin or they might not carry the particular dose that the prescriber has written. That has also resulted in delays or failure to fill the prescription.

Many pharmacies that our providers have dealt with may only have one pharmacist in that

facility that is registered. If they are not on duty to fill the prescription that day or log the patient in, then the patient has to come back and the delay is longer than 7 days, the prescription won't be filled. That has happened several times in my own practice.

Then, lastly, we have had some problems this past year with the month of February because it is not a 30-day month. That has also added some problems in that 7-day window and then 23-day lockout period.

Some of the things that we suggest is to consider using a computer-generated program with a date so that, once the patient is put into the system, that date automatically is generated by the computer so that the follow-up lab work, follow-up office visits, will automatically be computed, make it easier for the staff and the patient and maybe, if they had that printed out for them.

In addition to that, an intake sheet which would include a past medical history, review of systems and some further counseling might--

DR. BIGBY: Thank you very much.

The Chair recognizes the fourth Open Public Hearing speaker.

MS. JACOBSON: My name is Abby Jacobson. I am a physician assistant in dermatology in Lancaster, Pennsylvania. I have no conflicts of interest to declare.

Physician assistants, also known as P.A.s, are healthcare professionals licensed or, in the case that they are employed by the federal government, credentialed to practice medicine with physician supervision. Within the physician P.A. relationship, physician assistants exercise autonomy in medical-decision making and provide a broad range of therapeutic and diagnostic services.

P.A.s practice in every medical and surgical specialty. I am here today as Vice President of the Society of Dermatology Physician Assistants. Fellow members of the Society of Dermatology Physician Assistants work with Board-Certified or Board-Eligible dermatologists alone.

As part of our role in the team approach the dermatology care, the majority of P.A.s treat a large population of acne patients. Personally, I have an acne population that ranges from young adolescents to adults in their 50s and 60s.

I have seen first-hand how devastating severe acne or acne that is resistant to conventional therapy can be for these patients. Avoiding social events, low self-esteem and life-long scarring are only a few of the negative side effects patients share with me. I have had many patients literally reduced to tears as they explain to me how upsetting and demoralizing their acne makes them feel.

The Society of Dermatology Physician Assistants is dedicated to the appropriate use of isotretinoin. Isotretinoin is a life-changing, life-altering medication that significantly improves the quality of life for these patients ravaged by severe acne. We are committed to patient safety and to preventing pregnancies while taking isotretinoin through appropriate patient

monitoring and compliance with the tenets of the iPLEDGE system.

I personally believe that the changes made to iPLEDGE over the last few months are steps in the right direction. Changing the lockout period for men and for females of non-childbearing potential has greatly enhanced the use as well as continuity of care.

We have seen a significant improvement at our office in the ability to reach representatives at the Covance Center and I applaud these changes. However, there are still areas for improvement. As some of the speakers have discussed in the past, Roche had a program to provide medication for patients who could not afford isotretinoin,

Patients without health insurance or without prescription coverage could apply for free medication. The dermatologists and the P.A.s submitted the patient diagnosis as well as expected treatment plan to Roche. The medication was shipped to the dermatology office and we distributed it monthly to the patient. It was a

relatively simple process that greatly enhanced the quality of life for our uninsured or underinsured patients.

Under the current iPLEDGE system, there is no access for these patients to receive this medication. Many millions of Americans do not have insurance or are underinsured and have severe acne. We need to develop an avenue for these patients to receive this medication.

I also support a change to the 23-day lockout period for women of child-bearing potential. Many of my female patients of child-bearing potential who have been locked out at some point during their therapy when we then try to reauthorize the medication, their insurance will deny that because we have had preauthorization greater than five months ago.

If we resume therapy and that refill prescription is then denied, by the time the pharmacy notifies us of the denial, we then appeal to the insurance company. Once again, that patient may be locked out again for seven days.

Even after repeated attempts to explain that the patient never underwent a completed five months of therapy, some insurance carriers are continuing to refuse to reauthorize isotretinoin for these patients because some of the companies state in their policy that a 2-month rest period must occur between courses of isotretinoin. In the end, my patients are frustrated and they ultimately receive an inadequate dose of therapy.

These are just two example of where the iPLEDGE system needs to improve. The Society of Dermatology P.A.s is committed to working with Covance, committed to working the FDA, committed to working with the manufacturers of isotretinoin to improve the iPLEDGE system.

Isotretinoin is a life-changing, necessary medication for patients who suffer from severe acne. We must work together to ensure public safety as well as beneficial access to this medication.

Thank you for your time.

DR. BIGBY: The Chair recognizes the fifth

public speaker.

DR. HEBERT: I am Dr. Adelaide Hebert. I am here to represent the Society for Pediatric Dermatology. I am the immediate Past President of that organization.

The Society for Pediatric Dermatology supports the FDA's efforts to prevent intrauterine exposure to oral isotretinoin. The members of the society wish to promote the proper and safe use of oral isotretinoin in both on-label and off-label uses for patients.

The Society for Pediatric Dermatology recognizes the challenges in creating and maintaining a system to allow the use of this medication to do the most good and the least harm to the patients for whom it is prescribed.

Pediatric dermatology patients may use unique challenges with regard to the use of iPLEDGE Program. Disorders such as neonatal acne, ichthyosis ranging from the harlequin ichthyosis, the collodion baby, bullous and non-bullous ichthyosiform erythroderma, lamellar ichthyoses,

pityriasis rubra pilaris and psoriasis are typically first recognized during childhood.

There are few, if any, double-blind placebo-controlled studies that guide practitioners in the ongoing treatment of these disorders. Many of these cutaneous conditions lack FDA-approved drugs or listed devices to allow physicians to manage these disorders optimally.

I would like to illustrate for you some of these challenging disorders that we treat as pediatric dermatologists.

I do want to reiterate the information provided by Dr. Diane Baker. I think her statements reflect very carefully those also of the Society for Pediatric Dermatology. I reiterate as well that teenagers with acne or others with nodulocystic acne carry both internal and external scars from that disease if not adequately treated, the vast majority of patients treated by pediatric dermatologists with isotretinoin or those with this form of nodulocystic scarring acne. It is, indeed, a very serious disorder and there are few drugs

that, in four or five months of therapy, can truly change a person's life the way that oral isotretinoin can.

We have a number of disorders, as I mentioned, that I am going to cover. Cystic acne can occur in infants and this may lead to lifelong scarring. It is effectively managed with isotretinoin. I realize this slide may not project perfectly but this child does have very severe acne.

There are a number of ichthyoses that are very severe disorders that we do treat, not on an ongoing basis, necessarily, with oral isotretinoin but, on occasion, when it is necessary. This child's life was virtually saved with oral isotretinoin therapy. This child has the harlequin ichthyosis.

These are additional slides of that patient.

This is a collodion baby who suffers ultimately with a form of ichthyosis known as lamellar ichthyosis. Here are some slides

illustrating that condition.

This is a youngster who remains in my practice. He was a baby at this point. Here he is with his very thick altered cutaneous surface. Here he is as a little bit older child. Here he is just a few weeks ago in my clinic with a scarring alopecia and very widespread cutaneous disease.

I want to show you some of the other ichthyoses. These are very severe skin conditions that we treat in pediatric dermatology, again, not necessarily with ongoing doses of oral isotretinoin but sometimes with intermittent dosage under special circumstances.

Childhood pityriasis rubra pilaris is a very painful condition. This child's feet are virtually 100 percent denuded because of this condition and this child cannot walk and screams because of the pain on a daily basis that it suffers because of this skin condition.

Here is an older child with this condition who can't effectively use her hands for school or play activities.

This is a child who is 16 who has very severe pustular psoriasis, misses school, starts off her day normally and winds up with lakes of puss that result in daily admissions on a fairly regular basis. There are currently no systemic agents that are FDA-approved for treatment of psoriasis in this pediatric age group.

How can iPLEDGE be more effective for those of is in pediatric dermatology? Perhaps, we continue with the educational programs but we design a registration and education program that is best suited and most efficient for male patients and pre-pubertal patients who have special needs, and we certainly want to facilitate the use of oral isotretinoin for those special patients who have non-acne indications for this most important medication.

Thank you. I have no conflicts of interest.

DR. BIGBY: Thank you very much. The Chair recognizes the sixth speaker. Is the seventh speaker here? Okay. The Chair recognizes the

eighth speaker.

MS. PAHL: Good morning. I am Tish Pahl, a principal at the law firm of Olsson Frank Weeda Terman Bode Matz. I am speaking today on behalf of the Healthcare Distribution Management Association or HDMA.

Thank you for this opportunity to comment on the iPLEDGE Program. HDMA is a trade association that represents approximately 40 full-time service healthcare distributors including national, regional and small family-owned businesses. By way of disclosure, these HDMA members have business relationships with isotretinoin manufacturers.

Today, I will discuss the role of wholesale distributors participating in the iPLEDGE Program and the interconnection between the distribution of an individual drug in such a risk-management program and a multitude of other drugs in the supply chain.

Given this interconnection, I will also describe why it is important to ensure that any

requirements established for a single drug, specifically isotretinoin, have minimal impact upon the distribution of other drugs in the supply chain. We also have recommended improvements for iPLEDGE Program.

The average wholesale distribution center is essentially a large warehouse. It holds hundreds of thousands of individual saleable units of drugs and healthcare products which are purchased from over 500 manufacturers. A typical D.C. takes orders and arranges for shipment of almost 60,000 products each day to hospitals, retail pharmacies, clinics and other dispensing sites.

On average, one distribution center will maintain arrangements to ship the 750 locations. Almost 80 percent of the nation's prescription drugs are handled through the wholesale distribution system. In total, HDMA members deliver 9 million healthcare products nationwide to more than 144,000 dispensing sites each day.

The wholesale distributor maintains lists

of its customers. If there is a change in the status of any of those customers in the processes or computer systems used to order, pick, pack and ship products to those customers or, in the software used to maintain this information, the distributor must make any such change very carefully to ensure accuracy and to avoid inadvertently affecting or delaying the ordering and delivering of the hundreds of thousands of other products stored in the same warehouse and tracked by the same systems.

Immediately upon learning about iPLEDGE in late 2005, HDMA worked with FDA isotretinoin manufacturers, Covance and the other affected parties, to resolve a variety of operational and logistical issues and concerns.

Our goal was to ensure that distributors could participate in the program without disrupting the supply of the millions of other products they distribute each day. Our limited time today won't allow me to fully describe those extensive efforts wholesale distributors undertook before iPLEDGE

began.

Instead, I will describe some of the ongoing efforts that are in place and that set our recommendations in context.

Although each HDMA member operates independently depending on their business needs, most perform at least some of the following actions as iPLEDGE participants. Distributors must maintain computer systems and software to compare internal customer lists to the list of activated pharmacies that Covance provides each day.

They must do this without disrupting the efficient delivery of the other 60,000 products shipped from the same distribution center and tracked using the same systems.

Some distributors use automated product ordering systems. This means the distributors must reset these systems each day to allow newly activated pharmacies to place isotretinoin orders and to prevent non-activated pharmacies from placing orders for the products.

Distributors also point out and help

resolve discrepancies found in the activated pharmacies list. For example, if a pharmacy believes it is activated but is not listed as such, distributors also train warehouse, IT and customer-service staff to understand the isotretinoin operational procedures and computer-system changes and to be able to help their pharmacy customers with the iPLEDGE Program in ordering.

Distributors must make additional arrangements with common carriers to accommodate the short turn-around delivery requests that are inherent in the program. Some distributors have purchased new software and other systems to accommodate these new iPLEDGE procedures.

While these processes and procedures support the continued and safe efficient supply of isotretinoin products, they also require, obviously, a considerable amount of staff time.

I will turn now to the potential iPLEDGE data reporting requirement which remains a significant concern for wholesale distributors. We

are referring to the anticipated requirement for wholesale distributors to report information about the purchasers of isotretinoin products and the quantities purchased.

We believe the intent of this requirement is to analyze order information and pinpoint possible discrepancies and errors. It is, as we understand it, the wholesale distributor who would have to provide this data and that the pharmacies' reporting would be voluntary.

We are concerned about this voluntary reporting policy because we believe it would be virtually impossible for distributors to implement it. If only partial reporting is required, or if the reporting is voluntary, wholesale distributors would have to go through several steps to sort the tightly controlled isotretinoin product data from the other product data and to separate the confidential data from the data that are cleared for reporting.

This will require a careful examination of tens of thousands of data points daily. We are

uncertain as to whether such a process is even technically feasible. But, at best, it will require additional staff time, expensive, sophisticated data-analysis tools and other significant investments. This is a concern because it is being used to sort orders for one single product.

Requiring this level of effort in an industry where profit margins tend to be less than 1 percent may, we believe at HDMA, force distributors to reevaluate their participation in the iPLEDGE Program.

Moreover, partial reporting will probably result in meaningless data because the compliance tracking systems will not be able to fully identify the exceptions. Should this data reporting requirement become a reality for distributors, HDMA has several recommendations to overcome our concerns.

Specifically, data for all pharmacy participants should be reported. There are existing methods for transfer of data including the

867 Electronic Data Interchange, or EDI, transaction set which is a standard for this type of data and shows product transactions or sales.

If data release is voluntary for some iPLEDGE Program participants--if, for instance, pharmacies are able to choose whether or not to permit the release of their transactional data--then reporting should likewise be voluntary for all iPLEDGE participants including wholesale distributors.

If permission to release the data is voluntary for pharmacies but reporting remains mandatory for distributors, then the only alternative we believe is to send all the product transfer data to Covance or to their agent who would then extract the data from the pharmacies who have permitted its release.

There are additional technical issues that would need to be resolved prior to establishing these final data-reporting requirements including the fact that not all distributors have an EDI transaction capability. In addition, these

capabilities do not necessarily record the same data or in the same fashion. Confidentiality, security and other operational complexities would also need to be addressed.

HDMA has a few additional recommendations, among them, since iPLEDGE distributors must ensure that isotretinoin products are only ordered by and shipped to activated pharmacies, participating distributors have limited ability to perform warehouse-to-warehouse transfers. Such transfers are needed to further support the rapid distribution of products and the iPLEDGE's tight time constraints.

We would like to see a mechanism for including registered wholesale distributors on Covance's daily pharmacy list.

Finally, we recommend allowing distributors to request and use the pharmacy's iPLEDGE activation notification letter as documentation that the pharmacy has joined the program. This would reduce the delay that occasionally occurs when a pharmacy receives

official approval to dispense isotretinoin. But they have not yet appeared on the updated pharmacy list from Covance.

In conclusion, HDMA is committed to working with FDA, Covance and the sponsors and all affected parties to resolve these issues. I welcome any questions.

DR. BIGBY: Thank you very much. The Chair recognizes the ninth speaker.

DR. STRAUSS: Thank you, Mr. Chairman. My name is John Strauss. I am currently an emeritus professor of dermatology at the University of Iowa in Iowa City, Iowa. From 1978 to 1998, I was head of the University's Department of Dermatology. I am a past President of the American Academy of Dermatology. I have also been a lead investigator in many multi-center studies on the use of isotretinoin in the management of severe treatment-resistant acne and my bibliography contains many articles on the use of isotretinoin for severe treatment-resistant acne.

After my retirement, I was a consultant

for Hoffman-LaRoche for three years but I have no connection with the company now and, therefore, no conflicts of interest to declare.

I am a firm supporter of all the programs that the manufacturers and the U.S. Food and Drug Administration have instituted over the years to prevent pregnancies in women taking isotretinoin. I emphasize the prevention of pregnancy to my patients, to the residents I teach and to various health professionals to whom I lecture. To the best of my knowledge, no patient under my care has become pregnant while taking this medication and I have been using the drug since 1978.

I requested to be a public speaker for the American Academy of Dermatology and for myself before I saw Dr. Susan Walker's FDA background package as well as the industry briefing document for this meeting two nights ago.

While I am very pleased that most of my concerns are addressed in these documents in that the 23-day lockout is being eliminated for all patients except for the first month for women of

child-bearing potential, I still see problems that I hope will be considered.

As background, let me state that, for me, because of the 30-day lockout, the essentially 30-day lockout, my management of isotretinoin-treated patients has been difficult since iPLEDGE was instituted.

Like many other physicians, I have a fixed schedule and the 30-day lockout makes it impossible to follow patients, yet I am a nationally recognized expert on the use of isotretinoin. Removing the lockout for males and women of non-child-bearing potential has helped as will the removal of the lockout for all women except during their first cycle.

I think I understand why 30 days are used. It is because the drug is dispensed in 30-day packages. However, in real life, patients are seen in week intervals and, in the case with isotretinoin, that is 28 days, not 30 days. This represents a quality-of-care issue.

At the same time, I would like to request

that serious consideration be given to flexibility and timing of allowable prescriptions for isotretinoin under special circumstances. I will cite two such circumstances.

First, many of my referral patients who present with difficult dosing problems require adjustment at more frequent intervals than 30 days which is impossible under the current iPLEDGE system.

Second, a year ago, a tornado did considerable damage in Iowa City. A sorority house in which one of my patients lived was destroyed and, as a result, my patient lost her isotretinoin. I presume it is floating somewheres over Kansas.

In spite of our repeated requests, the iPLEDGE system prevented the patient from obtaining a new prescription until the full 30-day period between office visits had expired. This inflexibility constituted a serious quality-of-care issue in that the interruption of continuous care directly interfered with my patient's therapy.

In summary, as an advocate for my patients

who need isotretinoin therapy, I want to assure that patients receive the best possible care without compromise. I can live with iPLEDGE but the time sequences need to be more flexible and take into account realistic patient scheduling.

Thank you for allowing me to present these concerns, ones that should be easily corrected. I would be pleased to answer any questions. Thank you very much.

DR. BIGBY: Thank you very much.

The Open Public Hearing portion of the meeting is now concluded and we will no longer take comments from the audience. The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

I would like to take the prerogative of sort of allowing another half an hour of qualifying questions and then, at that point, we will stop that and start deliberating on the questions.

**Qualifying Questions and Answers (Continued)**

DR. BIGBY: I did, honestly, put myself in

the schedule so I get to ask the first question. The first question we are going to have to address is about the changes that are proposed and we are supposed to discuss whether the proposed changes are acceptable.

Would somebody like to clarify, for me, how it is going to work if the 23-day-lockout period for females of child-bearing potential are allowed after that time elapses to reapply. So, what I really need to know is you said they have to get another pregnancy test. Does that mean they have to have an office visit? The doctor has to interact with the iPLEDGE system? The patient has to interact with the iPLEDGE system and then they can get a new prescription filled, or does that just mean--what does it exactly mean will happen now that you have dropped the 23-day lockout?

MR. SHAMP: Jim Shamp, Covance. You are correct. What that means is that each of the requirements that the prescriber and that patient have to do to qualify for a new prescription must be completed again. The prescriber must provide

the counseling and confirm that counseling of the patient in the iPLEDGE system.

That patient must have another CLIA-certified lab pregnancy test result. The prescriber must enter those test results into the system and that patient must answer her comprehension questions.

Those steps all lead up to the qualification for that prescription.

DR. BIGBY: Thank you. We are going to go on with people asking qualifying questions. I would urge people to keep them to qualifying questions at least for the next half hour and try not to ask a ton of questions.

The next questioner is Dr. Kramer.

DR. KRAMER: Actually, my questions were posed by other members of the panel. Thanks.

DR. BIGBY: Next on the list is Dr. Skinner.

DR. SKINNER: Thank you. I just have two quick questions. The first one is is there any data on the pregnancies per month and how it has

been going? I know that the average is about 10 a month with this first year, but is there some trend that it is lessening. Dr. Baker says things mature and the system goes on. Does it work better or do you have any graph on the pregnancies and when they have been reported?

DR. RESHEF: Dan Reshef from Hoffman-LaRoche. Yes; we have the information of pregnancies distribution by month. If I may have, please, the slide up.

[Slide.]

What you can see on the screen is actually a tally of the pregnancies by month beginning with March of 2006 and all the way to the latest four months that I had mentioned earlier in my presentation.

DR. BIGBY: In reality, we can't see anything.

DR. RESHEF: I think they are trying to adjust that.

DR. BIGBY: We will hold that. If you get that slide fixed, could you put it back up.

The next questioner is Dr. Sawada.

DR. SKINNER: I had one more question.

DR. BIGBY: Oh; I'm sorry.

DR. SKINNER: This is for Covance. I noticed that, in this data on, "told to avoid pregnancy," although it is 99.7 percent, there are about 1,200 women of child-bearing potential that seem to have gone through the system and not been told to avoid pregnancy. I wondered how that developed. Also, in the women who actually get pregnant, about 1 percent had said they were told to avoid pregnancy. I was wondering how that happens with this system.

DR. RESHEF: Dan Reshef from Roche. I believe your question is based on a calculation of the number of women that were not responding positively to the baseline survey. Is this what you did?

DR. SKINNER: Yes; was told to avoid pregnancy, there is about 1200 women that, I guess, in there that were not told to avoid pregnancy. It is a higher percentage, I think, with the women of

child-bearing potential that actually got pregnant.

DR. RESHEF: Right. If I may have the slide up, and this is a slide from my primary presentation.

[Slide.]

Unfortunately, this is not yet--okay. As you have seen in the presentation, and I believe you have that material in front of you, the slide shows the percentage of positive responses of women--this is the feedback from the women. It does not reflect, in fact, if this counseling was offered by the healthcare provider. So it has the limitations of a survey. And yet the percentage that report positively, as you can see, is pretty high.

DR. SKINNER: No; I agree it is high. But 1200 women not being told to avoid pregnancy is 1200 women that could get pregnant.

DR. THIERS: Could I just make one comment. I think, Rob, what he is saying is because they said they weren't told doesn't mean that they weren't told.

DR. SKINNER: No; I agree with that. But there are 1200 women that somehow got through the system and didn't realize they were told not to get pregnant when the system is designed to avoid pregnancies.

DR. BIGBY: Can you go back and show that monthly slide that didn't project before as well.

MR. SHAMP: Jim Shamp, Covance, if I may address that specific last question. The question that was asked that we are talking about right now is actually one of the baseline survey questions. There is no right or wrong and getting the authorizing of the prescription is not dependent upon you answering this question with a yes.

It is truly just to record what the patient recalls as having occurred with their interactions with the doctor. So it is possible that the patient answered, no, I don't remember getting counseling or being told not to get pregnant from the prescriber and she will still get her prescription.

DR. BIGBY: Can you go back and show that

monthly slide now that we can probably see the numbers.

DR. RESHEF: Yes. Dan Reshef. Please, slide up.

[Slide.]

This looks much better now, I think. The table shows the pregnancies as reported by month in the first year of iPLEDGE. In addition, we have added the latest four months that are beyond the Year 1.

DR. BIGBY: Thank you. The next questioner is Dr. Sawada.

DR. SAWADA: My question was, I know that the manufacturer has said that they would pay for contraceptive counseling if the patient so desires. I was wondering if you have the data as to how many females of child-bearing potential actually took you up on that and took up that payment for contraceptive counseling.

DR. RESHEF: Dan Reshef from Roche. I would like to remind you of the slide in the primary presentation. Slide up, please.

[Slide.]

I would repeat the explanation. In fact, there is a specific question addressing this; from whom did you receive the birth-control counseling. In the table, you can see the numbers and the relative proportion of the non-pregnant females of child-bearing potential as well as the pregnant women that have received this birth-control counseling from another healthcare provider.

DR. BIGBY: The next speaker is Dr. Day.

DR. DAY: Related to that, do you have data on the types of people who were "others," the designees in the program. A physician can counsel and do all the surveys and so on, and anyone else in the practice that he or she so designates.

I have talked to some medical assistants who do this. My understanding is that they can be wonderful care givers but often have no college degree. Some hire other medical assistants and want them to have no background so that they, the other medical assistants, can train them.

This is critical because not only are

patients having trouble understanding the material, as we will discuss more fully later when we propose some changes, additional changes, to the program, but I think that the caregivers in the practice have some challenges in understanding some of the materials

One example from the root-cause analysis survey, some of the questions, they are wonderful--it is a wonderful scope of things that are asked. So at least a third to a half of them violate well-known linguistic principles that make it difficult to understand.

For example, one of the questions is about, you are not sexually active, and you have to answer yes or no. I mean, so there are double negatives and so on and so forth and there are easier ways to do it.

So perhaps the 10 percent completion of the RCA survey has to do with the difficulties in administering it as well. So it is really important--and it started today with Dr. Mitchell who did ask about the other providers. Do you have

data about the distribution of people in the system in the physician's office and what their positions are.

MR. SHAMP: Jim Shamp, Covance. But first I would ask a clarifying question. When you are talking about these other physicians or stakeholders in the office, are you talking about providing the counseling, the monthly counseling, to the patient or the referral to another healthcare provider for specific contraception counseling?

DR. DAY: Not the referrals. Anyone who interacts with a patient around any of the elements of iPLEDGE, all the surveys, the comprehension questions all the way to the root-cause analysis survey.

MR. SHAMP: All right. Thank you. We allow two different types of stakeholders for a prescriber's office to be registered. The first is the prescriber and the second is an office-staff designee. The intent of the office-staff designee is that they are allowed to enter data on behalf of

prescriber into the system.

The prescriber is ultimately responsible for the entry of that data so we do have a distinction in the system between the prescriber and the office-staff designee.

It is prescriber's responsibility to provide that specific counseling to the patient whether or not office staff designee confirms that counseling in the system.

DR. DAY: That was not my question. I appreciate the answer. But what proportion are medical assistants with no background training, P.A.s, who are highly trained, nurses who are highly trained, et cetera--the question is simply do you have data about who the designees are, relative proportions and so forth.

MR. SHAMP: I apologize for misunderstanding your question even after I attempted to clarify it for myself. Upon registration, we do collect that data from the stakeholders as to the type of practitioner that they are. So we do maintain that data.

DR. DAY: It would be valuable to know about that in future reports.

DR. BIGBY: The next questioner is Dr. Nelson.

DR. NELSON: I actually have two questions as well. In the presentation, you talked about two providers being deactivated. And, in the preliminary information, the briefing document that was sent around, there just happened to be prescribers who falsified pregnancy-test data.

I assume that those are the same two people. If that is so, or even it is not, I would just be interested in knowing how widespread this process is, if we think that this is the tip of the iceberg or if these are just two renegades that kind of just slipped through somehow.

MR. SHAMP: Jim Shamp, Covance. One of those two prescribers is representative in that other number. The one prescriber that was deactivated was deactivated for entering false pregnancy results. The other was deactivated because they provided a patient assistant old drug

in the office to a patient.

The other prescriber that you saw listed in the presentation earlier today, there was actually an office-staff designee that entered false pregnancy results on behalf of a prescriber. We did follow up and do our noncompliance process with that. The sponsors were satisfied with the prescriber-specific actions that he or she took with that office-staff designee such that we did not deactivate that prescriber.

DR. NELSON: But is there any way to know if this is a widespread practice and they just got kind of caught or if this is just these two people and it has never happened any other time.

MR. SHAMP: We do not have data to point that this is a widespread problem.

DR. NELSON: Right. But I wonder if there is a way to do some sort of quality-assurance process to make sure that this is actually not a widespread process.

MR. SHAMP: I would certainly be open to suggestions that we could then discuss with our

Scientific Advisory Board on ways to determine that.

DR. NELSON: Yes; because it seems like quite an egregious--

DR. BIGBY: Can I ask just a quick follow-up question on that? How did you determine that pregnancy-test results were falsified?

MR. SHAMP: Jim Shamp, Covance. It was a result of follow up from the reporting of the pregnancy in discussions with the patient. She indicated that she had had the pregnancy test and that the prescriber had entered a false result prior to obtaining the actual result.

DR. NELSON: My second question is more of a comment, perhaps. I wonder--although, I don't know this off the top of my head, but I assume that the period teratogenicity of isotretinoin is probably the second trimester of pregnancy. Is it the first? And it is early in the first. Because I would wonder, based on when it was, whether there is a way to kind of change the perspective of determining pregnancy to be from something that

seems very punitive in the patient's mind to being something that might be more of a carrot rather than a stick which would maybe enhance their participation in the RCA, make them not feel like they did something terrible but, perhaps, make it feel like we are trying to support them and do something to help them out.

It might be too late at that point. I don't know. But it is certainly something to consider, just the approach to the way we word these things.

DR. BIGBY: Did you want a reply to that? No? Dr. Platt is recognized.

DR. PLATT: The comments, the public comments, about lack of privacy protection were disturbing. I would appreciate comments from Covance about the accuracy of those comments, and comments from the agency as well would be appreciated.

MR. SHAMP: Jim Shamp, Covance. As you heard from the public speaker that we have revised our privacy statement and it now more closely

reflects the actual practice. Our practice always has been, as well as the sponsor's, that we do not share any data for marketing purposes.

Any data that is shared is only shared with the sponsors and the FDA and the data that is shared with them is de-identified. There is no identifiable data.

One additional thing. The revision to the privacy statement is at the FDA right now for their review and, once that review is completed, we will be posting that on the website.

DR. PLATT: And for FDA as a general proposition or are privacy issues part of the RiskMAP development procedures?

DR. WALKER: Would you like us to address the privacy issue? We, of course, would be very concerned about any violation of patient privacy in this type of a program and we will work with all the stakeholders to make sure that we become very clear on this issue. So any specific instances of privacy violations we would very much appreciate those being reported to us.

DR. BIGBY: The Chair recognizes Dr. Gross.

DR. GROSS: Two questions. Number one, when the manufacturers are asked a question, how do you get the slides up so quick? [Laughter.] I guess you can tell us later.

The second question is is there any clustering among the prescribers for not doing what they should be doing in addition to the two people who were eliminated. The issue where patients say they don't recall or maybe did not actually get information on pregnancy prevention, which is sort of hard to believe but I guess it happens, is there any clustering among prescribers who are not doing the job right and, if there is, is anything done about it to educate them or remove them from the program.

MR. SHAMP: Jim Shamp, Covance. I will, once again, attempt to clarify. I apologize if I get it wrong. But I believe you are asking if we have looked at data based on the survey results to see if the same patients that answered, perhaps, no

to the same question had the same prescriber; is that correct?

DR. GROSS: Yes.

MR. SHAMP: No; we have not looked at that data to that level of detail, but that would certainly be something that we be very interesting to perform.

DR. BIGBY: The Chair recognizes Dr. Mitchell.

DR. MITCHELL: Two questions. One is you mentioned the Scientific Advisory Board. It wasn't presented in any of our materials. Do you have the membership of that and what their role is in the project?

Actually, while you instantly putting that slide on, as I am sure we will discuss in the later part of the session, you can implement system aspects only so far in terms of human behavior, but the system is presumably designed to prevent one kind of pregnancy and that is exposure to an already pregnant woman.

There were ten such pregnancies identified

that you described to us, three of them for explained reasons, two deception a provider. But the seven that got through the net aren't described. Could you also let us know how those seven got through this net which seems to be so tightly drawn?

MR. SHAMP: Jim Shamp, Covance. Slide up, please.

[Slide.]

This slide and the slide following this does represent the membership of our Scientific Advisory Board. I will allow my colleague to respond to your second question.

DR. RESHEF: Dan Reshef from Roche. I believe the second question had to do with the ten women that started isotretinoin when they were already pregnant; correct?

DR. MITCHELL: Yes.

DR. RESHEF: Could I please pull the slide up.

[Slide.]

This is a detailed account of these ten

women. Let's go through this. One prescriber entered the false-negative pregnancy test that actually was mentioned earlier. In one instance, a designee entered the false pregnancy test results and this was also mentioned by Mr. Shamp.

It looks like one patient had access to drug from a previous program from years ago. Another patient claimed a false-negative pregnancy test result. In fact, she was pregnant. For the other six that you have focused on, there are issues around the timing of the pregnancy test in relation to the menstrual period of this particular individual patient. There is the relative timing to the unprotected sexual intercourse.

As we all know in the scientific world, there are some inherent test limitations. We are talking here of single cases from a population of close to 100,000.

DR. BIGBY: The Chair recognizes Dr. Thiers.

DR. THIERS: Two questions. I just wanted to go back to the public testimony again, with the

caveat that this is my first meeting and some of these--at least this first issue may been addressed.

In terms of the testimony regarding--involving wholesale distributors and the data collection, is there any evidence that that would make this a more effective program, because we have been given data on why women got pregnant, what were the circumstances.

Is involving the wholesale distributors in collecting all this data--is there evidence that that is going to make this a better program or is this just adding regulation upon regulation because I personally see no point in collecting data just for the purposes of collecting data.

If it is not going to help this program be more effective, why are we asking them to do this. That is my first question. Anybody who has more seniority here can answer that.

The second question was Dr. Strauss. When he mentioned that there is a 4-week follow up or a 28-day follow up rather than a 30-day follow up,

John, I just wasn't sure what you were proposing when you mentioned that. So maybe you can clarify that.

DR. STRAUSS: Am I allowed to speak?

DR. BIGBY: You are, indeed.

DR. STRAUSS: It is not clear to me, Dr. Theirs, whether, with the 7 plus 23 which equals 30--whether I can get that patient back in four weeks or whether I have to wait to 30 days. If I wait to 30 days, say I see patients on one day of the week, I can't see them again because they are outside the limit. And that is not clear to me. Maybe Covance can clear it.

MR. SHAMP: Jim Shamp, Covance. With the 7-day window plus the 23-day lockout, that does equal to essentially a 30-day lockout. You cannot provide counseling and confirm that counseling in the system until after that time has expired. So you must wait until the expiration of that 23-day lockout today to start the process over again.

DR. STRAUSS: And that interrupts therapy by physicians who have assigned days in their

private practice or in their institutional practice. That is the point.

DR. THIERS: Then the other question is why we are asking the wholesale distributors to collect this data which I think is already available from the pharmacies.

MS. PAHL: To respond to that, this is Tish Pahl on behalf of HDMA. Doctor, we share your skepticism as to the requirement. In defense of all who are concerned, we are not currently implementing this. We understand that it was a part of the initial program and that its implementation has been delayed until other aspects of the program are up and running.

We note that, in the briefing materials that were distributed in advance of this meeting, the summary of the program, that this data-reporting requirement for distributors was not included or discussed in it and we welcome its absence.

If, however, this program element does reappear in iPLEDGE, then HDMA simply wishes to be

involved in those discussions with FDA and other stakeholders.

DR. KWEDER: This is Sandra Kweder from FDA. The issue of how closely closed the system needs to be in terms of distribution remains unresolved and we are working with the sponsors to assess the relative merits of various ways of doing that.

However, I think it is important to keep in mind that when the program was developed, one of the key components that we and the advisory committee had great concerns about was the ability of pharmacies to opt out of the program.

Pharmacies that could obtain product from a source other than a registered wholesaler or distributor could easily opt out of program and make the drug available to patients and patients wouldn't have to participate in the program.

These are very difficult--once we get into the whole area of distributors and wholesalers, this is a whole new world. It is not an area that most medical doctors know anything about. But we

are looking into it, working with the sponsors, to find ways to assure that the only pharmacies that can prescribe isotretinoin are those who are participating in the program.

DR. BIGBY: The Chair recognizes Dr. Kresel.

DR. KRESEL: Actually, my question is similar to Dr. Thiers but goes one step further in going back to the issue of the lockout. I understand what we are going to be looking at, and so I am being very pragmatic here, is we are looking at only leaving lockout period in for the first cycle of women of child-bearing potential and eliminating for all other patients.

But, if the 30 days is not practical and does not address office needs, does not address 28-day months, 30-day months and 31-day months, would it make more sense to have a 21-day so you have 21 and 7 and have a 28-day lockout. I don't think that would be--it doesn't sound to me like that change would be particularly difficult.

Since I don't practice dermatology, I am

not sure that it makes a difference but it sounds like it does. Being pragmatic here, if we are going to make a change, let's try to make one that actually suits people.

DR. BIGBY: Did you want a reply or that was just a suggestion?

DR. KRESEL: Well, what I wanted was a reply to does that make sense. What was the reason for strictly keeping it to 30 days and does 28 days make more sense?

MR. SHAMP: Jim Shamp, Covance. I want to make sure I understand your question. Are you asking if we should not, instead of eliminate the 23-day, just shorten it to a shorter time period?

DR. KRESEL: No. As I understand the question that is being posed is we are talking about eliminating the lockout period which has already been eliminated for men, has been eliminated for women of non-childbearing potential. We are talking about eliminating it for women of child-bearing potential except for in their first drug cycle; correct?

MR. SHAMP: That is correct.

DR. KRESEL: So my question is does it need to be a 30-day lockout or does 28 days make more sense.

MR. SHAMP: For the first cycle?

DR. KRESEL: For the first cycle.

MR. SHAMP: The lockout for the first cycle, and I am going to clarify again, this is if you miss that first prescription and you are locked out; is that correct?

DR. KRESEL: That's right. And then do you wait 21 days so that it is 28 and allows four weeks because I do understand that a lot of people see patients on Tuesdays and Thursdays, or whatever, and so it doesn't fit their schedule if it is not an even integer.

MR. SHAMP: The lockout in this specific case, which is the exception to the removal of the 23-day lockout is for an additional 12 days because the 7-day window with our changes will start with the collection of the pregnant test. We know when you have the first pregnancy test, the 7-day window

has expired. We lock you out an additional 12 days which is a total of 19 days to satisfy the package-insert requirement of the two pregnancy tests at least 19 days apart.

DR. KRESEL: So this is, then, a moot point. Okay. Thank you.

DR. BIGBY: I think we should go on to discuss the questions. If people have additional clarifying questions, I think you should just incorporate them into your comments about the questions.

**Questions to the Committee**

The first thing I need to know is, Susan, given what has transpired up to now, do you want to keep the questions the same?

DR. WALKER: Yes; we would like to keep the questions the same. Thank you.

DR. BIGBY: Clearly, 2 and 3 don't require a vote. Are you interested in a vote on the first question or just the discussion?

DR. WALKER: I think a discussion with a consensus is appropriate. But, if this is

disagreement, we would certainly be interested in having a vote. We would like the opinion of the committee on whether we should or should not approve the supplement.

DR. BIGBY: Okay. Let me just read and reiterate the first question. The changes proposed in the pending supplement are intended to increase program flexibility and to reduce interruption of treatment. Please discuss whether the proposed changes are acceptable.

I think what I will do is I will start over here with Jimmy Schmidt and we will just go around the table from there.

DR. SCHMIDT: We already do a lot of this stuff in my office where we don't put in the date of the visit. We wait until we get the pregnancy test later. So, actually, a lot of this with the lockout periods is a moot point.

But, basically, I agree with all of these changes, the change in the lockout periods, as being something that is a very positive step.

DR. BIGBY: Dr. Day. I also understand

that you want to show us a couple of slides.

DR. DAY: FDA has suggested I share something with the committee. Would this--

DR. BIGBY: Absolutely.

DR. DAY: I am Ruth Day. I am a member of the committee. As I said, FDA has suggested I share this with you.

[Slide.]

This is from the recent public meeting on medication guides--

[Slide.]

--and is just some excerpts relevant to this meeting. This is research funded by ARC through the Search Program.

[Slide.]

We studied comprehension of the Accutane Medication Guide. I am not picking on one particular product. That was the name of the guide at that time.

[Slide.]

The basic method was a study test paradigm. After people studied the medication

guide, we tested all the contents on multiple cognitive tasks including attention, comprehension and memory.

[Slide.]

One of the key educational messages; we asked, what is the most important information I should know about Accutane--excuse me; that is what the medication guide says. That is one of the main first questions.

[Slide.]

There are three things that people should know about, that they should not take the drug if they are pregnant, plan to get pregnant or get pregnant while taking the drug.

We are now going to plot percent correct. 96 percent of people knew they should not take it if they are pregnant. What if they plan to get pregnant? About half. And what about if they get pregnant while taking the drug? Zero.

Why was there zero here? We can trace this result and many others in our study back to the nature of the information that is provided.

[Slide.]

Let's look at sample patients from the medication guide.

[Slide.]

Here it says, in the original format, who should not take Accutane.

[Slide.]

Since it is hard to see, I will blow it up for you. It says, do not take Accutane if you are pregnant, plan to become pregnant or become pregnant during Accutane treatment.

[Slide.]

We have made an enhanced version--

[Slide.]

--where we make time zones. So what you should know and think about before taking and then while taking. This is a big distinction in people's minds because they can read everything up front but it is while they are taking that they need to know something and we can relocate or duplicate the information about become pregnant during taking it down to the "while" time zone.

And this does enhance comprehension.

[Slide.]

So, a final comment about research methods and testing methods within the program. For example, in the RCA, there are questions about, did you understand about this, and so forth.

Ordinarily surveys test perceptions, opinions and attitudes whereas a carefully controlled laboratory experiment tests comprehension, memory and other processes. So we are looking at cognition here, the process of knowing, and most of what the testing is about is about meta-cognition. Meta-cognition is the process of knowing what we know and how we know it.

[Slide.]

Our research shows that, when you test meta-cognition, what people think they know, both just after studying the materials and then later after we test them, that there is something very interesting going on.

[Slide.]

One of the meta-cognition questions was,

how easy was it to understand the information in the leaflet. As you can see, they go down. They think that it was pretty easy before we test them and then, through the testing, they realize, well, maybe I didn't understand it so well.

The same thing happened when we asked them how easy would it be to remember the information from the leaflet.

[Slide.]

So the conclusions, just for us today, of just a tiny bit of this very large study; people overestimated how much they knew and understood after reading the medication guide. After testing, they realized that they knew less than they thought and the actually knew far less than that.

So, as we debate these three questions, they are all very important but I think we need to address the comprehension part of all of this. So many of these comprehension problems can be traced back to the materials and all are improvable and some are fixable.

Thank you.

DR. BIGBY: I was reminded that, for the comments portion here, please--you don't have to, and please don't, vote about it. I will just go around the room and have people comment on the questions and then we will take a vote after the comments are made.

Now, were those your comments on Question 1?

DR. DAY: No. My comments about the various proposed features, they seem fine to me subject to--yes; you can just put up that last--because there is a big gap between meta-cognition and cognition and that can be playing a big role in these 122 pregnancies. That was my final comment on that.

The proposed changes look fine to me and I may modify my views based on the dermatology experts who might be here.

DR. BIGBY: Dr. Mitchell.

DR. KWEDER: Michael, can I ask Ruth a question?

DR. BIGBY: Sure.

DR. KWEDER: Ruth, just to clarify who the people were that you studied. These were not people taking isotretinoin; is that correct?

DR. DAY: These were people who were self-identified as interested in treatments for acne and all self-reported that they either had acne now or had in the past.

DR. KWEDER: I guess the one question; was there anything in the study--because I know you didn't present the whole thing--that would address the issue of how would your knowledge--would this knowledge influence your sexual behavior and use of birth control.

DR. DAY: I don't have those data here with to discuss today.

DR. KWEDER: Okay. Thanks.

DR. MITCHELL: I also don't have any problems with Question 1 and I am really going to reserve my comments for the third question of which I will have many.

DR. BIGBY: Dr. Nelson.

DR. NELSON: I just have one question I

guess I am not totally clear yet about. But is this drug limited to prescription by dermatologists? This can be prescribed by anybody, I assume.

DR. BIGBY: Anybody is registered in iPLEDGE--

DR. NELSON: Because I sometimes--I guess I wonder about some of the limitations on the way the program is formatted for non-dermatologists, because dermatologists probably are more limited doing pregnancy tests in the office and what not, but some of the issues about CLIA certification and all. Maybe there is a long history to this and I just don't know it, but some of these laboratories, perhaps, that are in offices or in small buildings may actually be able to perform some of these tests.

DR. SKINNER: I would agree with these--I did some informal asking of practices of people who actually did the iPLEDGE system what their main problems were. I think this certainly addressed what everybody said. So I agree.

DR. SAWADA: I reviewed these changes and asked staff who are the ones who do the inputting what problems they are encountering. The only suggestion I have is the second item on, start 7-day window at the time of pregnancy test. I would like to say that, and/or at the time of the office visit because some of us have systems already in place--this would change how we do some things and so I would want to say that and/or at the time of the office visit.

The other thing, as far as Covance goes, is if we are requiring pregnancy tests, it sure would be nice to have access to, say, the urine pregnancy tests in the office, you know, free of charge. That makes it a little bit easier on patients who are already dealing with insurances and copays, et cetera.

That was just a suggestion.

Also, another suggestion was the call center issue. That still has some ways for improvement according to my office staff. I will reserve the rest for later.

DR. BIGBY: Since this is the comments section, I do have a few comments. The first one is, having uncovered in the iPLEDGE Program 122 pregnancies despite a fairly rigid program, making changes to make it easier to prescribe the drug may not be the politically intelligent thing to do. That is my first comment.

This has also been expressed, will the changes result in fewer pregnancies and a better program in achieving its aim is, I think, the major question here and sort of requiring physicians and patients to say they are using two forms of contraception does not mean that they do. And, even if they do, pregnancies will occur.

The described changes in the program, as far as I can see, will not decrease pregnancies. The one area that sort of bothered me when we created this and also now is that--and I actually didn't realize that this was a case that abstinence, by itself, is accepted as an adequate form of contraception. I think, 14 of the pregnancies, at least by the provider's

perspective, were failures to be abstinent. So I think requiring even abstinent women to have a second form of contraception, either the pill or morning-after pill, I think is a suggestion that actually would decrease pregnancies.

Then I am also surprised that there really is no verification of the pregnancy-test results. I had thought that that was part of the program.

DR. LESAR: Timothy Lesar. I don't believe the changes as delineated will improve safety, but I don't see where they will have substantial negative effects. I would just state that includes a number of areas of the program that could be improved.

DR. HENNESSY: Sean Hennessy. To the degree that the proposed changes to the program make it easier for patients to get the drug who should get it, that may reduce use outside of the system and could potentially increase the effectiveness of the program. So I am in favor of those.

I have a couple of quick comments. I

think that there should be metrics developed for the performance of the call center. I think that, although it is challenging, knowing the source of the 13 percent of the pregnancies that occur outside of the iPLEDGE system would be important to look at.

Then, finally, knowing the outcomes of the pregnancies, particularly for the large number of unknowns, again, while challenging, I think is very important to know.

DR. THIERS: I am certainly in favor of the changes. I don't think these changes will have an adverse impact on the number of pregnancies and I think it will certainly make the program more manageable. So I think we have something to gain and nothing to lose.

DR. KRESEL: I am also in favor of the changes. I would like to compliment both the FDA and the sponsors in keeping this as a dynamic process. I think it is really important that we keep this going.

While, on the one hand, you may say that

this is not necessarily going to prevent pregnancy, I think it is very important that we not waste resources on parts of the program that don't help either because we may, as the discussion goes on, find other places where we could use those resources more effectively.

This is a very expensive program and we should be spending our money for the best parts of it.

Finally, I am going to make the politically incorrect statement to say that I think we, as a group, have to make sure that we separate science from politics here.

MS. GRIFFITH: I am new to this particular issue and I would like to congratulate the FDA and the sponsors, too. I think that this iPLEDGE Program is remarkably comprehensive compared to other drug risk-management efforts that I have seen.

I would like to echo our Chairman's concern. When I looked at the number of reported pregnancies and looked at 14 resulted unsuccessful

at abstinence, one of the things that struck me in this conversation is tubal ligation doesn't exempt women from being categorized as females of child-bearing potential. I thought that that was rather odd to contrast that with abstinence. I would agree. I would like to see that--I don't know. These protocols may have been in place prior to this, but if the goal is to reduce the number of pregnancies, then I would also suggest that it needed to be backed up with a second form of birth control.

But I would also like to suggest that what Dr. Day proposed by just clarifying language is probably the most significant effort that could be made to convey what is significant about this program to the consumers and women at risk.

But, overall, I support the revisions and changes and think this is a very well-constructed, well-thought-out, program.

DR. KRAMER: I think that the proposed changes are all reasonable. This is also my first time in this committee. I must say, though, that I

have been struck that, when I read the materials and I read the questions, that I thought we were rearranging the chairs on the deck of the Titanic because the questions were all about improving this program but not addressing the question that Dr. Bigby raised and that is is the program having its intended effect of preventing pregnancies.

I realize that is very difficult. I think, even if we got to Ruth's point of having excellent cognition, we would still have the problem of cognition not relating directly to behavior as the FDA has raised.

But, ultimately, it seems to me that it is the responsibility of this committee to monitor that very carefully so that, I think, in the future, this committee should be presented the number of pregnancies with an analysis in writing to the committee of the pregnancy outcomes and, ultimately, should be addressing the question of whether the continued exposure to the public is acceptable.

So we were getting public statements from

people who think it is not and yet we are not discussing that. I don't think it should be implied and just make improvements around the edges, around things that will affect knowledge. I think we should be continually reassessing the big picture about whether this program is reasonable.

I realize there is tremendous medical need for this agent and I am sure the dermatologists all want it to be available. But we really must, to protect the public, continue to reassess this.

DR. DRAKE: I, too, would like to take this opportunity to congratulate everybody involved in this process. It is very complex. It is early in the process. If you think about it, it takes a while to work out the kinks and incremental changes work well. Congress has done that for many years, for example.

Incremental changes are a very sensible way to go and that appears to me what is happening today. So I am in favor of these changes. I think they are positive.

I would like to address the notion of are

we getting where we want to go. Well, I think we have to realize that if we increase compliance, because compliance is a huge issue in any part of medicine--if we can increase compliance, then we might, actually, then enhance our realistic goal, or enhance the success of the goal of reducing pregnancies.

So I think these changes probably will help compliance and, thus, hopefully, as we look at the data in the next few years, we will see that the pregnancy rate falls which is our ultimate goal.

I am interested in how we achieve a zero-risk population. The reason I really want to congratulate everybody involved in this, I couldn't help but thinking about this and this may be a politically incorrect thing to say, too, but I must admit--I was sitting here thinking about fetal alcohol syndrome. It causes very severe birth defects and yet there is absolutely zilch regulation on pregnant women drinking during pregnancy. Fetal alcohol syndrome is out there and

nobody is doing anything.

So I think what is happening here is extraordinarily positive and I would like to encourage us to follow some of Dr. Day's recommendations. I really liked what you had to say. I think too much paper is confusing. I think the linguistics are critically important. I believe all those issues will be addressed.

The other thing I wanted to say is that I want to--the one thing that hasn't been addressed, what was brought up by Dr. Strauss, are there any possible remedies or options that one might work with with emergencies or unexpected circumstances that give you unintended consequences.

Accutane is a drug, Accutane or isotretinoin or the generics. You need continuous therapy. To interrupt that is not fair to our patients. It does increase the risk. So are there any possible remedies--and I don't have an answer to it. I am just putting it on the table for people's consideration. Are there affidavits or is there any mechanism by which we could address some

unexpected emergencies that give us unintended consequences, and I don't know the answer to that.

Then, finally, I totally concur with the notion of confidentiality. I am very pleased to hear that issue is being addressed. I think it has to be. I don't think we should over-regulate and overburden manufacturers. I am in agreement with Dr. Thiers on that.

Thank you.

DR. WHITMORE: I don't have a comment about this but I didn't get to speak earlier so can I make a different comment?

DR. BIGBY: Absolutely.

DR. WHITMORE: Thank you. I was on the committee in 2005. The goal of iPLEDGE was stated to be to prevent all pregnancies. My comment then was, if we are really honest with ourselves, we will require a Norplant implant for the period of time--if that is our goal, to eliminate all pregnancies.

We all knew that the iPLEDGE Program could not prevent pregnancy. I thought one thing it

could do is prevent doctors from starting women who are pregnant on Accutane. The ten pregnancies that did occur, albeit for various reasons, that was one thing I thought was going to be zero. So that is a great disappointment.

The other thing, getting back to our goal to prevent all pregnancies, I think we should think about the possibility, since most persons who became pregnant realized that there was a failure of contraceptive use on the date of conception or did not use two forms of birth control or had unsuccessful abstinence, there was a realization at the time they conceived that they had been negligent in following through on this.

Thus, the thought of including Plan B with the initial prescription is something to consider, I think.

DR. PLATT: I honestly don't know how much confidence to put in the number of reported pregnancies because we weren't given any information on lost-to-follow-up. It was, frankly, surprising to me, that information isn't available.