DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Volume II

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8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

PARTICIPANTS

Peter A. Gross, M.D., Chair
Victoria Ferretti-Aceto, Pharm.D., Executive Secretary

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Terry C. Davis, Ph.D.
Jacqueline S. Gardner, Ph.D., M.P.H.
Eleanor Gomez-Fein, Pharm.D.
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Henri R. Manasse, Jr., Ph.D.
Robyn S. Shapiro, J.D.
Annette Stemhagen, Dr.PH (Industry Representative)

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Gerald Dal Pan, M.D., M.H.S.
Sharon Hertz, M.D.
Sandra Kweder, M.D.
Jill Lindstrom, M.D.
Paul Seligman, M.D., M.P.H.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. GROSS: This is a new day, so we are going to begin by re-introducing everyone. I would like to start off with Paul on the right.

DR. SELIGMAN: Good morning. Paul Seligman, Director, Office of Pharmacoepidemiology and Statistical Science, CDER.

DR. KWEDER: I am Sandra Kweder. I am the Deputy Director of the Office of New Drugs in CDER.

DR. DAL PAN: Gerald Dal Pan, Director, Office of Drug Safety at CDER.

DR. BEITZ: I am Julie Beitz, Acting Director, Office of Drug Evaluation III.

DR. CUMMINS: I am Susan Cummins. I am the Director of the Drug Safety Oversight Board.

MR. LEVIN: Arthur Levin. I am the Consumer Representative on the Committee.

DR. CRAWFORD: Stephanie Crawford, good morning. University of Illinois at Chicago College of Pharmacy.

DR. FERRETTI-ACETO: Victoria

Ferretti-Aceto. I am the Executive Secretary for the Committee.

DR. GROSS: Peter Gross. I am the Chair of the Department of Internal Medicine at Hackensack University Medical Center, and Chair of this Advisory Committee.

DR. DAVIS: Terry Davis. I am Professor of Medicine and Pediatrics at Louisiana State University Health Sciences Center in Shreveport.

DR. GOMEZ-FEIN: Eleanor Gomez-Fein. I am a pharmacist at Jackson Memorial Hospital in Miami.

DR. MANASSE: Henri Manasse, Chief Executive Officer of the American Society of Health System Pharmacists.

DR. GARDNER: Jacqueline Gardner, Professor, University of Washington School of Pharmacy.

DR. FURBERG: Curt Furberg, Professor of Public Health Sciences at Wake Forest University.

MS. SHAPIRO: Robyn Shapiro, Director of the Center for the Study of Bioethics at the

Medical College of Wisconsin, and Professor of Bioethics.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I do drug safety research at the University of Pennsylvania.

DR. STEMHAGEN: I am Annette Stemhagen from United BioSource Corporation. I am an epidemiologist, and I am the Industry Representative to this committee.

DR. GROSS: Thank you, all.

Victoria.

Conflict of Interest Statement

DR. FERRETTI-ACETO: I will be reading the Conflict of Interest Statement.

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that

all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions:

In accordance with 18 U.S.C. 208(b)(3), Dr. Peter Gross has been granted a waiver for his membership on an unrelated Data Safety and Monitoring Board for one of the affected firms. He receives a fee of less than $10,001 per year. Dr. Gross has also been granted a waiver for his ownership of stock in an affected firm valued between $5,001 to $25,000.

Dr. Henri Manasse has been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock valued at less than $15,001. Because the stock interest falls below the de minimis exemption allowed under 5 CFR 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

Dr. Terry Davis has been granted a waiver for her ownership of stock in two affected firms.

The stock values are between $5,001 to $25,000 and $25,001 to $50,000. In addition, Dr. Davis has been granted a waiver under 21 U.S.C. 355(n)(4), an amendment of Section 505 of the Food and Drug Administration Modernization Act, for ownership of stock valued at less than $15,001. Because this stock interest falls below the de minimis exemption allowed under 5 CFR 2640.202(a)(2), a waiver under 18 U.S.C. 208 is not required.

A copy of these waiver statements may be obtained by submitting a written statement to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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

With respect to FDA's invited Industry Representative, we would like to disclose that Dr. Annette Stemhagen is participating in this meeting

as a Non-Voting Industry Representative acting on behalf of regulated industry. Dr. Stemhagen's role on this committee is to represent industry interests in general, and not any one particular company. Dr. Stemhagen is employed by United BioSource. Due to conflicts, Dr. Stemhagen has been recused from participation in the committee's discussions of the risk management program for isotretinoin products.

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

Open Public Hearing

DR. GROSS: At this particular point in the agenda, we will begin the open public hearing. Before that I need to read the statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing

session of the Advisory Committee meeting, the 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 any company or any group that is likely to be impacted by the topic of this meeting,

For example, the financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, the 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.

Can we have speaker number 1, please, and the name will appear on the screen.

MR. COCHRAN: Good morning, everybody. First of all, I have no financial encumbrances as far as this meeting is concerned. As much as I would like to say I own a lot of stock in different drug companies, I do not.

I am Tim Cochran. I am the Associate Director of Industry Relations for Healthcare Distribution Management Association, HDMA, located in Arlington, Virginia, and I am here to talk really on the iPLEDGE program regarding isotretinoin distribution.

First, I should say I appreciate the opportunity to go ahead and give you some perspectives from my company, HDMA, and its members on the progress of the iPLEDGE program and provide a couple of recommendations for future considerations by FDA and this group.

For those who are not familiar with HDMA, we are the national trade association representing primary, full-service distributor companies in the healthcare industry, and we are responsible for ensuring that billions of units of medication are

safely distributed to tens of thousands of retail pharmacies, hospitals, clinics, nursing homes, and other provider sites every day, and this is across the 50 states and the U.S. territories.

As government licensed entities, healthcare distributors ensure product safety and provide the vital link between manufacturers and healthcare providers by warehousing finished product, processing orders, keeping records, managing inventory, and providing other services as required.

On any given day, our members deliver more than 9 million healthcare products to 142,000 healthcare sites, and this nation's pharmaceutical distribution system provides a ready, reliable source of medications for patients when they need them most, in times of illness and medical need.

HDMA members provide the essential function with little public recognition and visibility, but they provide a great savings to the healthcare distribution system of our country.

On behalf of HDMA and my colleague, Anita

Ducca, our Senior Director of Regulatory Affairs and Healthcare Policy, who happen to have been instrumental in providing distributor feedback to help develop and improve the iPLEDGE program, we are very appreciative of the opportunity to have worked with HDMA staff, the manufacturers, sponsors of the program, and the other various industry stakeholders, such as NACDS, the National Association of Convenience Drug Stores, and the National Community Pharmacy Association, NCPA, in overcoming problems, the initial challenges faced with the combined iPLEDGE program.

Although we feel several issues remain to be fully addressed, we commend the cooperative tone set by the FDA staff towards developing an efficient and effective risk management program.

I have noted the scope of the distributor community's role in assuring safe and reliable delivery of pharmaceutical products, to emphasize the very significant processes that have been put in place to manage this effort.

A program such as iPLEDGE or similar

programs need to take into account the systems and processes used by the distribution supply chain, or implementation can be unnecessarily disruptive to the flow of prescription medicines, it can be unduly expensive as far as the exception processing that might be needed for specific distribution of a product, or, in the worst case, it may cause a distributor to make the difficult business decision that it is not a product that they can actually carry, and that would be of course in no one's interest.

Several of the outstanding challenges we believe still remain involve reporting of sales and shipment data for the isotretinoin products. We have worked diligently with the FDA, the sponsors, and the manufacturers' representative, Covance, to discuss these issues, and look forward to further communication regarding potential resolutions.

We also look forward to the opportunity to review the forthcoming iPLEDGE compliance plan from Covance. HDMA certainly understands the importance of this program succeeding, and certainly commits

to work with the FDA and other industry stakeholders to that end.

As far as recommendations, we would urge that in the creation of future risk management programs such as iPLEDGE, that HDMA and other representative organizations of the distributor community be invited to participate in the discussions on program requirements and operational issues very early, on the earliest stages of the processes of that development.

HDMA actually only learned of the iPLEDGE program in August of 2005, which was really just months before planned implementation. Given the critical role that distributors are asked to play in this program, and the highly complex nature of the healthcare distribution industry, we urge that in the future, the Committee, FDA, the manufacturers, and all other stakeholders seek the input at the very beginning of the process.

We believe that early involvement in key decisions, including those by this committee, would benefit all parties while supporting our mutual

objective to provide these products to the patients that need them.

In conclusion, HDMA commends the FDA, Covance, and the sponsors, and the other partners in the pharmaceutical supply chain for outstanding efforts to support the distribution, dispensing, and use of isotretinoin, and I thank you very much for the opportunity to speak here today.

DR. GROSS: Thank you, Mr. Cochran.

Speaker number 2, please.

DR. THIBOUTOT: Good morning. My name is Diane Thiboutot. I am the Chairperson of the American Academy Dermatology's Task Force on Isotretinoin.

In terms of disclosure, I also serve on the Scientific Advisory Board for Covance with regard to the iPLEDGE program, but I have received no honorarium nor financial support from them. I also have no conflicts with the manufacturers of isotretinoin.

My travel here today has been paid for by the American Academy of Dermatology.

I didn't realize that Tim was speaking today on behalf of HDMA. The American Academy of Dermatology also takes part in the iPLEDGE program. I hadn't planned to address it, but my point is the same basically, that from the beginning we have had little to no opportunity to provide input into this very critical and very large system, this very large risk management system that has been put in place.

The main purpose of my visit here today is to, in a public forum, ask for the opportunity to have a delay to the mandatory start date of March 1, 2006 of the iPLEDGE program for a variety or reasons which I will enumerate today.

The information that I will convey today has been conveyed in previous avenues to representatives of Covance, as well as representatives of the manufacturers, and some aspects of it have been also given to the FDA, as well.

I understand that today's session is an informational session, and later today you will be

hearing more about the iPLEDGE program, however, you are not going to hear from the prescribers' perspective how this program has been affecting the prescribers in practice.

Before I begin, I would just like to call attention to some of the documentation that you might have. I looked on the web site, and you probably have been provided with the isotretinoin risk management program in part of your packet.

If you call attention to page 3 of that risk management program, where it outlines the clearinghouse responsibilities for the iPLEDGE program, if you are able to find them, the Item No. 1 in terms of the clearinghouse responsibility is to provide a secure system.

The system is quite secure, in fact, to the point that prescribers and patients are having difficulty accessing it.

Point No. 2. The system should be user-friendly, real-time, rapid, direct, accessible, and available 24 hours a day. In the information that I will provide to you today, I

think you will realize that perhaps this objective has not been met.

Item No. 3 is to ensure that health professionals and other staff are accessible to talk to patients and rapidly address any concerns or problems with the registration, qualification, or approval process.

I think that the information that I provide to you today will indicate that Item 3, the objective has not been met. Furthermore, I have a question in regard to where is the quality control for the clearinghouse process. I understand that there is internal quality control, but I am unaware of external quality control, and I am concerned as this program mandatory start date is scheduled for March 1st, 2006.

I would like to briefly read a prepared statement less than half a page, and we also have received over 200 testimonials from prescribers across the country that have been coming to the Academy's office.

Yesterday, we asked for input from the

Dermatology Nurses Association, and requests for additional information was put out, and within a 24-hour period, the President of the Derm Nurses Association received over 150 e-mails outlining the difficulties that have been encountered in the practice setting.

As you know, the iPLEDGE system goes beyond regulating a drug to really regulating the practice of medicine. Under previous programs, prescribers have adjusted their practice patterns to comply with the regulations.

Prescribers are now attempting to adjust their practice patterns to comply with iPLEDGE, but are failing because they have not been provided with the necessary details to incorporate the iPLEDGE program into their practice, and furthermore, they are failing in their attempts to get the needed information and materials from the iPLEDGE call center or web site.

The system is cumbersome and many of its components with regard to males and females who cannot become pregnant are illogical and appear to

be dictated by the confines of a computer program.

Prescribers have been asking for operational details since last August. These have not been available in advance, because we were repeatedly told that this system, for reasons that we are yet to understand, was being rolled out in a just-in-time fashion with little to no opportunity for input on the part of the stakeholders.

In effect, although this was not originally intended, prescribers have had the opportunity between January 1st and now to begin to utilize this system. Rather than work out the problems in test sites, as recommended by the Academy last fall, all practices and all pharmacies and all wholesalers in this country have in effect been serving as test sites since January.

The results to date are a disaster. Pharmacies, prescribers, and patients are confused and frustrated. Waits on the phone lines of over an hour are occurring. Patients and prescribers are locked out of the web site. Repeat visits to doctor's office are occurring in attempts for

patients to get prescriptions. Patient care and safety are being compromised, the very things that the program is designed to prevent.

First impressions are lasting impressions. If the mandatory start date of March 1st is not delayed to allow prescribers and patients the necessary information and details to comply with this program, there will be significant dropout at all levels, forcing frustrated patients and families to purchase the medication on the Internet, because they have been unable to obtain it through their physician, whose attempts to work within the system have failed due to the mandatory implementation of a known operationally flawed system.

The scope and magnitude of the difficulties in implementing this program at all levels, wholesaler, pharmacy, prescriber, and patient, have been grossly underestimated. We do not see that additional resources, such as call staff or rapid improvements, are being made to the web site to help remedy this situation.

We urge you, as representatives of the FDA, that in the interests of patient safety and with the interest of any potential future success of this program, to delay the mandatory start date of March 1st for two months in order to provide prescribers and patients the details and the materials needed to adjust their practices to comply with this program.

I would now like to read just a couple testimonials from some of our prescribers. These are ones we have received from our web site.

I want to relate my experience with attempting to register a patient with the iPLEDGE program. I do not use the Internet in my office, so I first attempted to use the automated phone system. I punched in my ID and then my password. I was told that the two did not match, so I tried again with the password that was given to me. Again, no match. I called back and my only option was for talking with a person was to press the option for a patient wishing to register with the program.

I was given a case number, transferred, and after waiting on hold for quite a while, I was cut off. I tried again. I explained my situation to the operator. She implied to me that she would let me speak with a supervisor, but instead attempted to give me another case number. I had no more time.

I took the patient information home. I logged on to my home computer. I entered the data. I was given another number, but no option to submit it. This patient remains unregistered.

I am very frustrated with this and I am at the point very reluctant to prescribe isotretinoin as I have fears that treatment might be interrupted by my inability to register patients. I feel that the deadline must be extended until the kinks are worked out of the system and it becomes user-friendly or just usable.

Comment No. 2. I was just registering a female isotretinoin patient and came across a glitch in the program. After registering the patient, I proceeded to the Managed Patient Section

to confirm contraceptive counseling. It asks you to enter the date of the counseling. I entered the date of the visit, which is when I counseled.

Next, you enter the date of the visit. I entered yesterday's visit date because this is when the visit occurred. It gave me a message that the date I entered was invalid. I called the iPLEDGE system and was told that the program only allows you to enter today's date as the visit date even if you saw the patient yesterday.

Comment 3. The problem is that with the new system called iPLEDGE, it is not workable in its current form. My staff and I have spent over 100 hours trying to help our patients get their needed medication. Unfortunately, we have not been able to register and treat our patients despite carefully following all of the new FDA guidelines. Thousands of physicians across the country are having the problem.

One of the main problems is that all of the details needed to use this computer system are not available to prescribers. There is no help

section on the web site and for us to try to get answers to the questions, the waits on the phone can be very long, an hour, two hours. You are oftentimes put into an answering machine where you might get a call back that day or you might get a call back three days later.

In order to use the system, we need to know the rules that we need to use it.

I could go on for a long time, but I am not going to. I just want to share with you some of the cases and some of the people from my practice that this system comes under their jurisdiction.

The main problem is lockout. We are not able to use the system. We are trying, we haven't been provided with the materials that we need. These are the patients that we are treating.

If you look at this young gentleman, if this child were your son, you would have a concern. He needs to go to high school every day. He has this appearance. Isotretinoin is the only medication that will help a child like this. If

you can imagine, if this child is not able, despite his best efforts to get his medication through his physician, these kids are computer savvy. He is going to go to the Internet. He is going to find another way to get the medication.

This system needs to be halted as of March 1st, we need to have the opportunity to give the system a chance and to make it work.

This is acne scarring. Acne scarring is a very rapid process. When someone has acne to the degree that these patients have, every day counts. This computer system locks patients out for a 23-day period or a 30-day period, and right now the way that the program is happening is that patients and prescribers are being locked out due to system failure, not due to the fact that the doctors aren't trying, not due to the fact that the patients aren't trying.

Patients need a password. They have to get their prescription within a 7-day window. Oftentimes the password isn't arriving at their home until 7 to 10 days later. How are they going

to get their medication in a 7-day window when they haven't gotten their password?

If you wait another 23 days, you are running the risk of scarring.

Another patient. You oftentimes don't see people like this on the street anymore because of the medication isotretinoin. I understand its problems, I am fully aware of its teratogenic potential. I am embarrassed that in the past perhaps that people were not complying with the measures that they should have complied with. I feel very strongly about that.

For any chance of this program to have success, the prescribers and the patients need to be aware of the rules. We are willing to abide by the rules, but right now we don't know them.

Another example. You can see that patients with appearance such as this can be quite bothered psychologically and physically by this problem. If this computer system is not as in the program guidelines, if it is not user-friendly, if it is not real-time, and if it is not available 24

hours, 7 days a week, the problem with diversion is going to occur.

Again, I would like to urge you to delay the mandatory start date of March 1st.

DR. GROSS: Thank you, Dr. Thiboutot.

Next on the agenda is to hear from Dr. Gerald Dal Pan about Office of Drug Safety Updates.

Office of Drug Safety Updates

DR. DAL PAN: Good morning and welcome back to day two of our advisory committee.

What I would like to do is just take about 10 or 15 minutes to update the committee on some new developments in the Office of Drug Safety that occurred since our last meeting in May 2005.

[Slide.]

The first thing I want to update on is the Office Leadership. The office now has a new permanent Director. That is me. We also have an Acting Deputy Director, Dr. Jonca Bull.

Many of you know our Deputy Director, Dr. Anne Trontell. Dr. Trontell has gone on a one-year detail, which is government speak for a temporary

assignment, to the Agency for Healthcare Research and Quality, where she is Senior Pharmaceutical Outcomes Advisor in the Center for Outcome Effectiveness. She hopefully will learn a lot there and we look forward to her coming back in a year to share what she has learned with us.

In addition to myself and Dr. Bull, our office leadership consists of Ms. Kathleen Frost, who is our Associate Director for Regulatory Affairs.

I am also pleased that Mr. Ralph Lillie, who was the Acting Director of the Office of Drug Safety from January of 2005 through late November 2005, when I took over, has agreed to stay on, and his role will be really organizational and operational issues within the office.

In addition, Dr. David Graham, whom you heard yesterday speak, will continue in his role as Associate Director for Science and Medicine.

Earlier this week, we also announced to our staff that one of our senior epidemiologists, Dr. Judy Staffa, will be on a 120-day temporary

assignment in the Office of the Director, reporting directly to me, where she will coordinate our officewide research activities.

I will be talking about some of our efforts in these areas later in my talk. Dr. Graham yesterday also spoke about the contracts we have to do epidemiological studies. So, in her role, Dr. Staffa will be coordinating a lot of these efforts, and she will be working closely with Dr. Graham on the interface of science and epidemiology in our office.

[Slide.]

At the level of our divisions, we have three divisions in the Office of Drug Safety. That is unchanged. We have the Division of Drug Risk Evaluation, and that continues to be headed by Dr. Mark Avigan, who is the Director of that division.

Since our last meeting last May, a Deputy Director has joined that division. That is Dr. Rosemary Johann-Liang. She is a pediatrician and infectious disease specialist.

The Division of Surveillance, Research and

Communication Support was the division that I formally directed before my current position, and that is now in the hands of Dr. Tony Piazza-Hepp, who had been the Deputy Director, and is now serving as the Acting Director.

Finally, our Division of Medication Errors and Technical Support continues to be led by Carol Holquist and Denise Toyer.

[Slide.]

I am going to change gears a bit and talk about something that Dr. Galson announced last October, and this is some reorganization within the Center for Drug Evaluation and Research. This is a Center level reorganization, and it is not an Office of Drug Safety reorganization per se.

The goal of the organization comes out of the commitment of CDER to sustain multidisciplinary, cross-Center approach to drug safety.

Because of that, he wants drug safety activities placed in the organization in a way that reflects this high level of commitment. He also

recognizes the need for focus and consistency and improvement in communication about drug risks and benefits, and the need for focus for cross-Center policy development as this relates to drug safety.

Another goal of his reorganization is to find a home in the Center for what are known as critical path activities. These are activities for basically smarter drug development. The Office of Drug Safety is not a central part of that, so I won't be talking about that anymore. We are involved in it, but there are others in the agency who are taking the lead on that.

[Slide.]

So, as part of this reorganization for drug safety, Dr. Galson is creating a new position, an Associate Center Director for drug safety policy and risk communication, and he wants to consolidate certain risk communication activities that are currently spread across the Center.

Dr. Paul Seligman is leading the effort to create this office. It is important that this is not the Office of Drug Safety, and the Office of

Drug Safety will not be reporting to this Associate Director, but rather will be working closely with it.

With regard to the Office of Drug Safety, Dr. Galson will be elevating our organizational status to a direct report to the Center Director, so I will be reporting directly to Dr. Galson.

Then, as part of the critical path initiative, he is creating what is called a new "super-office," which is an umbrella office overseeing two offices, and OCPB is Office of Clinical Pharmacology and Biopharmaceutics, OB is the Office of Biostatistics, and this office will be responsible for the critical path projects and other cross-cutting scientific activities.

As I said, we will be working with them, but we won't have primary responsibility for this initiative in the Office of Drug Safety.

[Slide.]

Let me turn attention now to some of the database acquisitions we have acquired.

You heard Dr. Graham yesterday give the

results of a feasibility study from four different organizations with linked pharmacy-medical claims databases.

We signed these contracts in September of 2005, and what these contracts allow us to do is to have our epidemiologists work with epidemiologists and other experts at these organizations, to collaboratively work on their data sets to answer specific drug safety questions.

Those four organizations are the HMO Research Network at Harvard Pilgrim Health, the Kaiser Family Foundation, Vanderbilt University, and Ingenix or i3Drug Safety. Let me just go over what these databases are.

[Slide.]

The Harvard Pilgrim Health/HMO Research Network consists of eight HMOs in geographically diverse areas with a total membership of 3.2 million members. They have electronic medical records available for six of the eight sites. That goes beyond the claims data, but actual medical records electronically.

The Kaiser Family Foundation has data on 6.1 current members in northern and southern California. It has a fully integrated database and is linked to vital statistics and cancer registries.

It also has a unique formulary limited to selected drugs and indications.

Vanderbilt University combines data from two state Medicaid populations, the State of Tennessee and the State of Washington, has a total membership of 2.2 million members, some who are medically at high risk, such as the poor and nursing home residents.

Ingenix, or i3Drug Safety, has a geographically diverse insured population of about 12 million members. They also have some laboratory data available which the others don't have.

So, you can see that these data sources are complementary to each other. What our contract allows us to do is work with the scientists and epidemiologists at these organizations to answer specific drug safety questions, so involves the

feasibility step that Dr. Graham discussed yesterday, basically asking the question do they have enough patients taking the drug of interest, do they have enough outcomes of interest, and will we be able to relate the two.

So, we would work with staff at one or more of these depending on the question to develop a protocol and conduct the research.

[Slide.]

We spoke last May about the upcoming Medicare prescription drug benefit and the data source, that that may be an additional data source to us, and our epidemiologists have been working with the Center for Medicare and Medicaid Services, as well as the Agency for Healthcare Research and Quality staff to understand better the nature of CMS data.

As a Medicare Part D, the prescription drug benefit just went into effect, so there is no data in that database now, so our current efforts are focused on developing a pilot study to use Part B data for a drug safety study largely to

understand the Medicaid data.

It is quite complex to work with, and we are working with AHRQ and CMS for our epidemiologists to understand it, and we are still in the learning/exploratory phases of that, so we don't have any results or anything concrete to report, but we are pursuing this avenue.

[Slide.]

We also spoke last May about active surveillance. Just by way of background, when we talk about MedWatch reports or reports on our Adverse Event Reporting System database, we are talking about a passive spontaneous surveillance system where we rely on patients and physicians and prescribers to send either to us or to the companies, to pharmaceutical companies, reports of adverse events when they observe one.

Companies, of course, are under an obligation to report those to us, so we have to wait for this information to come in, and active surveillance, we would want to identify data sources that we can actually tap into to see if we

can identify new safety signals before a passive surveillance system would bring them to us.

So, as part of that effort, we issued what is called a Request for Information in April 2005. That is where we asked the public tell us what is out there in this area, so it is not a Request for Proposal where you actually say we want to buy something, this is what we want to buy. This is one step before that. We just want to know what is out there.

We received the responses in June 2005, and the responses are still currently under review. It has taken a while to review them, largely because our epidemiologists, who are the main drivers for this effort, have been busy getting the epidemiology contracts moving, and they have also been busy with the CMS, but we hope in the next month or two to review them and then decide on what the next steps will be.

[Slide.]

Other Developments. We moved to White Oak. White Oak is the new campus for the FDA

consolidation located in Silver Spring. The Center for Drug Evaluation and Research will occupy two buildings there, and the first of those buildings was occupied late last summer, early fall of 2005. The second building, the foundation is just being poured now.

The Office of Drug Safety moved to White Oak in September of 2005 and all our offices are on the third and fourth floors of the D wing.

In addition to the Office of Drug Safety, many other CDER components moved out there including the entire Office of New Drugs, so now we are all in one building.

For those of you who aren't familiar with how we were geographically spread out, the Office of New Drugs was based in three different buildings. One was the Parklawn Building, the other was an office building about a mile and a half north of the Parklawn Building, and the other one was in an office building about 8 or 10 miles north of the Parklawn Building.

So, the day-to-day collaboration was

mainly by phone and e-mail. Now, we can have more in-person collaboration. I think that is a very positive benefit.

Finally, we have some, what are called "Process Improvement Teams." These are teams that are examining how we do our work and how we can do it more efficiently.

The Office of New Drugs has a Process Improvement Team examining its roles and interactions in postmarketing drug safety, and the Office of Safety has a Consult Improvement Team, which is examining the work products we produce in response to queries from people in other parts of the Center.

So, we are expecting to have some results from that in the next six months or so, and we will act on whatever improvements are needed to improve our process.

I think that is all I have. Thank you.

DR. GROSS: Thank you, Dr. Dal Pan. That sounds like important positive improvements.

We have time for some questions of Dr. Dal

Pan.

Yes, Annette.

Questions and Answers

DR. STEMHAGEN: I was wondering if you could just talk a little bit about your office involvement in risk management programs and strategies in developing them. Does that come out of New Drugs, does it come out of your group, or how is that coordinated?

DR. DAL PAN: The risk management program is a collaborative effort of the Office of New Drugs and the Office of Drug Safety. We coordinate a lot of these efforts in our office. We have a staff that reports directly to me, that coordinates risk management plans.

Risk management plans often involve, within the Office of Drug Safety, two or three of our divisions, so it's a cross-office function depending on the specific issues, because the plans vary, but then we also work closely with the Office of New Drugs on these plans.

DR. STEMHAGEN: So, do you get to review

all the risk maps that are part of the NDA filings?

DR. DAL PAN: Yes, we do.

DR. GROSS: Art.

MR. LEVIN: Just as sort of a follow-up on that. We heard some public testimony today that, if true, and I assume it's true, speaks to some disturbing operational issues about the risk management program for Accutane, that many of us were involved in, in recommending.

How would your office respond, I mean your joint collaborative effort with Office of New Drugs respond to this kind of problem in terms of the operationalizing of a risk management program having some unintended consequences.

DR. DAL PAN: I think with regard to the isotretinoin plan, the iPLEDGE, I think we are going to hear about that from Dr. Lindstrom later, and I think Dr. Kweder will be able to answer specific questions about that.

I think that is a broader issue. We are interested in developing methods to really understand, to really evaluate risk management

plans. I think that is something that we are trying to incorporate in all these plans, how to evaluate the effect of the plan, and that is an ongoing effort.

DR. SELIGMAN: Just one brief comment. Operationally, within the Center, though, there is a working group between the Dermatology Group in the Office of New Drugs and the Office of Drug Safety that works regularly, as well as in consideration of some of the concerns that were raised today, as well as those that have been written to us, they work as a working group together to jointly address those concerns.

DR. GROSS: Curt.

DR. FURBERG: I think we should applaud, commend you for the developments. I think what you are doing is strengthening your office, and there is probably still a long way to go.

We hear about you are understaffed. We heard about research projects that we can't fully support. Dr. Graham's study needs much more money to give us meaningful answers in a timely way.

We heard about the bottleneck getting the active surveillance programs analyzed and maybe funding. I mean it all comes down to funding as far as I can see. I mean that is the bottleneck for further development and strengthening your program.

So, could you comment a little bit about the funding situation, what the situation is today, and what are you doing to get more money, or is there any way that we can go on record supporting requests for additional funding?

DR. DAL PAN: Let me answer that in a stepwise way. We can always do more with more. That sounds self-evident, but it is also true. There is some additional money appropriated by Congress, an additional $10 million for drug safety in the '06 budget, and a portion of that is specifically allocated to the Office of Drug Safety, so we will be using that.

We haven't finalized how we are going to use that, but it will almost certainly be used to increase the number of staff we have, and if we

have some money left over, then, to go for additional data sources.

One of the things that we will be doing is really seeing how efficiently we can work, work as smartly as we can. We have a very, very dedicated, talented staff, and I am just going to try to make their working conditions as good as possible.

DR. SELIGMAN: May I make an additional point, Mr. Chair? As you know, Dr. Furberg, we are currently supporting a study being done by the Institute of Medicine, looking at drug safety and at the FDA, and one of the charges to that committee is to look at the way we are resourced, whether there is additional resources or the legislative authority or other things that we need.

There is certainly nothing to prevent either you or the committee from providing any information or suggestions or ideas to that Institute of Medicine group. They are certainly at a critical phase in their deliberations and any additions or ideas that you have, I think would be most welcome to them.

DR. GROSS: How should that information be provided to them?

DR. SELIGMAN: I can give you the contact information and the project officer for the Institute of Medicine.

DR. GROSS: Henri.

DR. MANASSE: I would like to pursue, Dr. Dal Pan, further the operational issues relating to drug distribution and restricted drug distribution, some of which we will get into in terms of the isotretinoin later on today, but my data suggests we have 26 drugs, biologics and vaccines that are now on some sort of a restricted drug distribution.

We should probably validate my information against yours, because I think the committee ought to look in a very comprehensive way the various and multivariate approaches that have been taken for restricted drug distribution.

As we have heard this morning from several of our speakers, and as we will hear later on today, restricted drug distribution, while it has good intentions, has significant operational

challenges at the level of practice, that is, practice of physicians and the practice of pharmacists.

As you might imagine, it is incredibly time-consuming and consequently, incredibly costly for whom no one pays.

What I hear from our 32,000 members, is that the pharmacy departments in hospitals are having increasingly to staff these restricted drug distribution programs, and, of course, that staffing competes with the normal work that goes on in pharmacy departments. Particularly in hospitals, that workload continues to increase given the acuity of patients and the intensity of drug use.

So, my suggestion is that the FDA sit down with those folks who are on the front line, and let's look at these 26 drugs more comprehensively and let's talk about perhaps new mousetraps that might be considered as to how we go in this direction.

My own prediction is that we likely will

add to the list of restricted drugs, and it seems that it would be more prudent and thoughtful to begin to work prospectively about how we manage this new kind of distribution system.

DR. DAL PAN: Thank you for that comment. I think we also recognize that there have been problems with some of these restricted distribution systems, and that is part of what the evaluation of risk management plan is about.

Better ways to do that, I think would be welcome. Do you have anything to add?

DR. SELIGMAN: I would just add I think your suggestion is an excellent one. I mean we have now accumulated sufficient experience through these various programs to I think now have an intelligent and robust discussion about what is working and what is not.

DR. KWEDER: I can give one example of where we have already begun to do something like this, but certainly not on the scale that we believe is needed.

Just by way of comment, until

isotretinoin, most of the restricted distribution programs with maybe one or two other exceptions have been single product, you know, single manufacturer distribution systems, which when you start getting into multiple manufacturers, and particularly taking drugs that were previously not restricted and restricting them in different ways, there is a whole different universe of considerations, which are responsible for some, but not all of the things that we have heard today, and we will talk more about.

But one of the things that is common to many of these programs is the need for pregnancy prevention, and we have certainly had much experience in trying to develop pregnancy prevention programs. A lot of these drugs do affect fetal development.

We are in the process of writing a guidance document for the industry to try to provide some advice and standards for how to put together in any distribution system where preventing pregnancy is important, some, you know,

helpful hints is one way of looking at it, but also establish some standards for what is acceptable and what is not, not enough.

DR. GROSS: Any other questions or comments?

DR. DAVIS: I have a question. This may be naive, but are restricted drugs available in an unrestricted manner over the Internet?

DR. KWEDER: Yes, they are in many cases. For almost any restricted drug, one can go to the Internet and find some source where one might be able to purchase that drug, or what is at least claimed to be that drug.

This is a very, very difficult problem. Most of the manufacturers of the legitimately restricted but distributed products, work to try and minimize that. They report new Internet sources to us. Many of those sources are international, and we really don't have a lot of control over them.

We try, our Office of Compliance spends a lot of time trying to identify sites and sources,

and do what they can to try and shut them down, but it is an uphill battle.

DR. GROSS: Important problem for the new world.

If there are no other questions or comments from the panel, then, Dr. Susan Cummins will talk about the new drug safety initiatives and the Drug Safety Oversight Board.

New Drug Safety Initiatives and the Drug Safety Oversight Board

DR. CUMMINS: Good morning. I want to thank you for inviting me to talk to you about the many new drug initiatives going on in the Center. You have heard about some of them already from Dr. Dal Pan, I will touch on them again, and I will focus on the Drug Safety Oversight Board.

[Slide.]

I want to begin just by giving a brief review of the drug safety landscape that we are living in right now, and then we will review Dr. Crawford's November 2004 announcement, Secretary Leavitt's February 2005 announcement, and then talk

a bit more about the Drug Safety Oversight Board, what it is and what its role is.

[Slide.]

First, I want to emphasize something that I know you appreciate, that drug safety is a top priority for all of CDER, and that that priority plays out at every stage of the product life cycle, both in the pre-NDA phase, all the way through the development and early marketing and review of new drugs, and into manufacturing and the regulation of drug quality in generic drugs, and in the regulation of clinical trials and promotional activities.

As you have heard, we are committed to doing more with more resources. It's a very important priority for CDER.

[Slide.]

It is such an important priority that in point of fact, half of all of CDER's work effort is focused and devoted to drug safety.

Many of you may not know this, but we do time accounting twice a year to look at how PDUFA

funds are being expended, and every staff member in CDER has to account for their time according to various kinds of work activities.

When we went back and analyzed the 2004 time accounting data, the data that has looked at actual effort by CDER staff, we learned that half of all CDER staff time is committed and devoted to drug safety efforts.

Of that 100 percent, 32 percent is focused on pre-market drug safety efforts, and that reflects the efforts over time to collect more safety data prior to marketing of a product, and 18 percent of that time is focused on post-marketing safety work efforts.

[Slide.]

Now, the drug safety landscape, I just want to touch on all the realm of controversy, because despite the fact that we are a regulatory agency with laws, with regulations, and with guidances that spell out in substantial detail exactly how we are supposed to address drug safety, this area remains an area of great controversy, and

I know you, with your specific expertise, can really appreciate that.

The bottom line is despite all the language efforts and spelling out exactly how we should focus on drug safety through laws, guidances, and regulations, there is the mix of science, judgment, and policy that plays into the controversy, and each of those areas has wiggle room that can create controversy about specific products or drug safety in general.

[Slide.]

So, despite all the rules, there is lots of room for honest disagreement. Honest, devoted, dedicated professionals looking at the same data can honestly disagree about how to interpret it or what its meaning is in terms of managing a specific safety issue.

They can disagree about how safe constitutes a safe product, that we have no single simple risk-benefit equation that we can apply to all products in a straightforward way and determine this meets the test of benefit versus risk, and

this drug does not.

There is always a tension between the drive for innovation and the development and introduction of new products versus the need for greater assurance of safety through larger and longer safety studies.

[Slide.]

This article from the Washington Post last April has two quotes which set these goalposts I think quite well.

The first from Representative Thomas Bliley from Virginia in 1995, who said, "It just breaks my heart when I think of American citizens having to go to Switzerland or Mexico to get the drugs and devices they need to stay alive because the Washington bureaucracy won't approve them."

Contrast that with this quote from Senator Grassley from last year saying, "When the FDA approves a drug, it should be a Good Housekeeping seal of approval. Consumers shouldn't have to second-guess the safety of what's in their medicine cabinet."

[Slide.]

Now, in 2004, Acting Commissioner Crawford announced a 5-point plan to improvement the management of drug safety concerns within CDER. I just want to touch on that plan now, so that you have an update on it.

You have heard first that we have sponsored an Institute of Medicine study of the drug safety system. That study is well underway. A report is due out in July of 2006, and just to emphasize the substantial national interest in this study, the first opening meeting of that Center was actually telecast on C-Span, which is a very unusual event at the Institute of Medicine.

The second was to implement a program for adjudicating differences of professional opinion. Differences can occur at the individual level among staff, and if they are not able to work it out between them, there is a process for resolution of those differences through the CDER Ombudsman.

At the organizational level, there is a difference of opinion between different

organizational entities within CDER, the classical example being a difference of opinion between the Office of New Drugs and the Office of Drug Safety. The Drug Safety Oversight Board is available for adjudicating those differences.

The third step was to appoint a permanent Director for the Office of Drug Safety, and as you know, Dr. Gerald Dal Pan was appointed in October of 2005.

The next step was to conduct drug safety risk management consultations. Those are underway, and I want to mention that last December, we held a Part 15 panel hearing to solicit input from the public about how we might best communicate with the public about specific drug risks, what might be most effective, how we are doing so far, and how we might make our efforts better.

Finally, there was a commitment to publish a series of risk management guidances, and those were published last spring.

[Slide.]

Three guidances were targeted to industry,

those are listed here, and one guidance was targeted to FDA reviewers, and established standards for how to conduct a clinical safety review, which is now a component of the Good Review Practice guidance for both new drug applications and biologic licensing applications, and it provides for standardization and consistency in how those reviews are conducted and how they are formatted.

[Slide.]

In February of 2005, HHS Secretary Mike Leavitt announced, in addition, a series of drug safety reforms, and he said in that announcement, "The public has spoken and they want more oversight and openness. We will address their concerns by cultivating openness and enhanced independence."

He also said, "We will keep the promise of the FDA brand by putting in place more rigorous oversight and collecting and sharing important and emerging information about drug safety and effectiveness."

[Slide.]

He committed to an overall vision of promoting a culture of openness and enhanced oversight within the agency, and outlined the specific areas of change by soliciting more outside expert consultations, by improving drug safety management practices, through communicating emerging drug safety issues early in the process of their evaluation, and by continuing to improve our scientific methods of adverse event signal detection through the establishment, for example, the establishment of the contracts that you just heard about.

[Slide.]

One major goal of this initiative is to give patients, healthcare professionals, and consumers quick and easy access to the most up-to-date and accurate information on medicines.

[Slide.]

Now, the drug safety initiative has several new information outlets. These include patient information sheets that provide, in plain, simple language to patients, key information about

specific drug safety risks, information to healthcare professionals about emerging drug safety risks with also the data and the information analysis we have to date on those risks, and also the proposed Drug Watch program, which I will touch on in a moment, and then again the Drug Safety Oversight Board. I will give you more detail on that next.

[Slide.]

Now, underlying this entire initiative is this important definition, the definition of an important drug safety issue. An important drug safety issue is one that has the potential to significantly alter the risk-benefit analysis of a drug, to affect a physician's decision to prescribe the product, or to end or to affect a patient's decision to use the product.

So, this is a broader definition than the regulatory definition of serious and/or life-threatening adverse event, but would generally, probably always include the definition, the regulatory definition of a serious and/or

life-threatening adverse event.

[Slide.]

Now, the Drug Safety Oversight Board was established to provide independent oversight and advice to the Center Director, so the board just says you advise CDER, the board advises the Center Director, and its charge is listed here, that it is to provide advice on how to manage important drug safety issues, it's a venue for adjudicating organizational disputes, as I mentioned earlier, it advises on policies about the management of drug safety issues and on risk communication about important emerging drug safety concerns, and on the development of the information sheets that I just mentioned.

[Slide.]

It has an overall closing charge, as defined in the Manual on Policies and Procedures for the Board, which I think you should have received as a handout before the meeting, that the role of the Board is to ensure that CDER decisions about a drug's safety benefit from the input and

perspective of experts both within and outside FDA who have not conducted the primary review or served as a deciding official in the ongoing pre-market evaluation or post-marketing surveillance activities for a specific drug.

[Slide.]

Now, this slide lists some of the key organizational principles. The first--and this has been one that I think has been confusing for many people--that the voting members are independent of the primary decision-making for a product with an important safety issue.

The Board membership consists of senior scientific managers within CDER, who have management responsibility for the overall work flow within CDER, but generally, are not involved in making specific product regulatory decisions, and in that sense, are independent of those specific decisions.

If, for example, for a specific issue before the Board, the member has played a very detailed and direct role in that decision, then,

they would need to recuse themselves from any voting that was done on one of those decisions.

The Board consists of all federal employees, but not all employees from CDER. There is an equal number of representatives from the Office of Drug Safety and the Office of New Drugs.

Twenty-five percent of the membership is external to CDER. That includes representatives from other FDA Centers who conduct related activities. That is the Center for Biologics, the Center for Devices and Radiologic Health, and there are also representatives from the National Institutes of Health, and practicing physicians from the Veterans Administration.

We also have the capacity to seek expert and/or consumer or patient consultants as needed for a specific issue.

[Slide.]

Now, here are just a couple other organizational principles I want to touch on. The concept of oversight is that the role of the Board is to focus on fostering effective CDER management

of important emerging drug safety concerns, looking at process steps that need to be put in place to assure that an issue is being managed and resolved appropriately.

Now, I want to make very clear, this has been an area of great controversy for which we have received many, many questions, that the Drug Safety Oversight Board does not replace advisory committees, such as yourselves. It doesn't even tackle or take on the kinds of questions that we bring to advisory committees.

It plays a different role. I like to think of it as a mindful structural management tool, a convening of senior scientists, managers within CDER, and additional federal employee experts that can advise us on how to move forward on complex problems.

Complex problems are ones that frequently touch on several offices within the Center, so just coming together to develop a path for resolution. It doesn't address the kind of technical, scientific questions that we bring to advisory

committees, such as should a drug be approved to put on the market, should additional specific safety programs be put in place.

It also does not replace the current internal structures and responsibilities for routine regulatory decision-making that take place every day within CDER.

[Slide.]

This slide lists the organizational membership. The Chair of the Board is Dr. Doug Throckmorton, who is the Deputy Director of CDER. Dr. Throckmorton is not a voting member, and I serve as the Executive Secretary.

The lists of CDER offices that are represented on the Board is there on the left, and I just want to point out that there are three representatives from the Office of Drug Safety and three representatives from the Office of New Drugs.

External to CDER, there are representatives from the Center for Biologics, for Radiologic Health, from the Department of Veterans Affairs, and the National Institutes of Health, and

our specific member comes from NCI.

I just also want to point out, because this has been also a question I have received often, that several of the CDER staff who are on the board are in medical practice, as well as the member from the Department of Veterans Affairs and the member from the NIH. So, we have several practicing physicians on the board.

[Slide.]

Now, at the time that the Board was announced, there was also the proposed Drug Watch. The Drug Watch was a web page on the CDER Internet site that would be a focus for provision of emerging important drug safety concerns that were undergoing evaluation within the Center.

The goal of the Drug Watch is to communicate about emerging risk issues to the public, so that that communication can inform their day-to-day treatment decisions.

A draft guidance for the Drug Watch was posted last spring. We received lots of public comment. We are in the process of reviewing that

public comment and revising the Drug Watch, and we anticipate that a new revised version should be published sometime this year.

[Slide.]

Now, much of the work of the Board initially has been on trying to conceptualize factors that we should consider when we communicate about an emerging safety risk.

These are the issues that have been suggested so far. First, if a risk meets the definition of "important drug safety concern" that I presented to you earlier, so if it might affect prescribing or monitoring, if there are specific measures that can be taken in response to the information to prevent or mitigate harm, for example, additional testing or monitoring.

If there is an unapproved or off-label use that we know about, that poses a significant or as yet undescribed risk, and I will point out a couple of examples of those in a moment, or if there are specific or vulnerable subpopulations that may be particularly impacted by that risk, such as

children or the elderly.

[Slide.]

Now, I just want to walk you through how to find this information. This has been again a point of confusion, and as we do not yet have a Drug Watch web site, it can be a little tricky to find the specific patient sheets.

I don't have a pointer, so I am just going to talk you through this. This is the CDER web page, I hope you all recognize it, and you will see in that mid-column--thanks--you see here in the central column, this big Drug Safety box.

If you click on this link about FDA's New Drug Safety Initiative, that will take you to a web page that has all the documents, the lists of the committee membership, et cetera, that describe the Drug Safety Oversight Board and related activities.

If you want to find the information sheets for specific products, you need to click on this link that takes you to the Drug Specific Information page, and I will show you that in a minute.

When we post a new set of sheets or a public health advisory about an emerging drug safety concern, currently, there will be a notice placed in this column, News from CDER, and if you scrolled all the way down to the bottom of this page, you could find a link to previous notices going back to 2005, and you could really pretty easily find the links that would take you to notices that are posted with new drug safety information.

[Slide.]

Now, this is the Drug Specific Information page. This is the page that has provided information about new molecular entities in plain language for the public since 1998, and interspersed between all these drugs are drugs that have had drug safety postings.

There is no as yet, because we don't have a specific Drug Watch web page, there is no way to go specifically to postings that have drug safety concerns, so you have to find them through the News at CDER page, or just check on the links to

specific drugs.

So, for example, if you were to click on the link to Accutane or isotretinoin, there is a link for both the trade name and the generic name, it would take you to a notice that would describe the iPLEDGE program that you are hearing about today.

[Slide.]

This is just a mock-up of a made-up drug that shows you the format for the healthcare professional sheets. They start with an alert at the top of the page that describes a summary, provides a very brief summary of the concern.

Then, there is a set of recommendations here for safe use. Those recommendations will generally focus on the issue that the alert is about. Then, there will be a data summary of the data known to date and the approach that FDA is taking to resolving the issue, a link to the approved labeling, a link to the patient information sheet, and a link to the MedWatch program, and contact information for more

information.

[Slide.]

This is the patient information sheet, and it has several differences from the healthcare professional sheet. The FDA alert is written often, but not always. As needed, it is written in simpler language, in plain language, so it is understandable to the public.

There is a link here to the healthcare professional sheet. There is a summary, basic description of the product with a box warning here if there is one. There is a link to MedWatch, to the drug information about the drug approval date, the date the sheet was posted, and then again contact information for the Division of Drug Information.

[Slide.]

As of December 31st, 2005, we had posted sheets on at least 44 drugs. These included 6 product class issues, 3 market suspensions for Palladone, Tysabri, and Neutrospec; 2 product withdrawals for Bextra and Cylert; and 37 products

that ultimately had added warnings about the concern that we posted to the product label.

[Slide.]

I mention that because there is a real tension between how do you and when do you warn. If we over-warn, if we raise a concern about minor problems, then, it really might discourage appropriate use of a product; if we under-warn, then, we don't provide information to patients and to healthcare professionals that might be useful in prescribing decisions despite its uncertainty at the point when we are providing it.

So, the Board has spent a lot of time trying to sort out and achieve and define the right balance.

[Slide.]

Now, as I mentioned, there are class risks that are described in several of these postings, and here are the class risks that have been listed for the antidepressants, the risk in suicidality in children, but also in adults.

FDA is undergoing a major re-analysis of

its existing data in the adult trials of all the antidepressants to look for suicidality signals, using the model that was developed for evaluating the risk of suicidality in the pediatric trials.

The atypical antipsychotics had a class posting about the increased risk of death when these products are used in adults with dementia. This is not an approved use.

There is a posting about the nonsteroidal anti-inflammatory drugs, both the COX-2s and the other NSAIDS about increased cardiovascular risk.

There was a posting about the erectile dysfunction drugs, and the occurrence of non-arteritic anterior ischemic optic neuropathy.

There was a posting about the topical immunosuppressant calcineurin inhibitors, Protopic and Elidel, a potential for cancer risk, and long-acting beta agonists, that there is an increased risk of severe asthma episodes that may lead to death.

[Slide.]

These are just several examples of

specific drug postings. Some of them you have already heard about, for Accutane, the new restricted access program is described.

For Paxil, there was a recent posting about the need to change, and the actual change in the label of the pregnancy category from C to D with new evidence of birth defects in infants, offspring of mothers who used Paxil during their pregnancy.

Strattera, atomoxetine, which is a nonstimulant drug approved for the treatment of ADHD, also was found to have evidence of increased pediatric suicidality, and we did a sheet about that.

Palladone, which is an extended release formulation of hydromorphone, was withdrawn because we learned shortly after it was approved that there was substantial dose dumping if Palladone was taken concomitantly with alcohol, and because it's a once-a-day dose and a very potent narcotic, there was a risk that if Palladone was taken with alcohol, that the entire dose could be released

very quickly and potentially cause death.

Campath, alemtuzumab, is a product that is approved for lymphoma, as an adjuvant therapy for lymphoma, but in a trial for multiple sclerosis, there was evidence of severe idiopathic thrombocytopenic purpura, and this is an unlabeled use, so we described those cases and recommended longer term monitoring of hematologic parameters.

Neutrospec was recently withdrawn because we learned after it was approved about these events of serious and life-threatening cardiopulmonary events that occurred very shortly after administration of the product, often within 10 to 15 minutes after administration.

[Slide.]

So, in summary, the Drug Safety Oversight Board has been established to: improve public knowledge of emerging important drug safety concerns; to strengthen internal drug safety management within CDER; to foster practical policy development that will improve the consistent approach of our processes for studying and

resolving drug safety concerns; for providing a standing venue for the resolution of CDER's organizational disputes.

It is not the whole solution or the whole answer to addressing drug safety within CDER, but is a central component of our overall initiative to improve the management of drug safety and to inform the public about emerging medication risks.

Many of the other components were touched on by Dr. Dal Pan in his presentation.

That's it. I wonder if there are any questions.

DR. GROSS: Yes, Henri.

Questions and Answers

DR. MANASSE: Thank you for a very informative update, and my congratulations in the case for all the thinking that has gone on in a relatively short period of time to move this issue along.

I have a couple of questions, the first one being how does the work of the Drug Safety Oversight Board bring in the safety and risk issues

associated with biologics and vaccines?

It seems that as we move scientifically, we likely will be seeing more of these kinds of agents, and there will be more than likely a serious concern on behalf of the public for risk and benefits, as well as safety, and I would be interested in getting your feel for how that gets integrated in this work.

DR. CUMMINS: That is a great question. The Board is a CDER entity, so it focuses on CDER products, so biologic products that are regulated by CDER would be the purview of the Board. We have not tried to tackle vaccines. That would probably need to, at this point, be handled by a separate entity for the Center for Biologics.

DR. GROSS: Can you give us some examples of issues that the Board has dealt with today?

DR. CUMMINS: The Board has spent a lot of time talking about risk communication, how to do risk communication, when we should warn the public, whether and how we should warn, what venues we should use for warning the public, how we should

communicate about that, what factors we should fold into those discussions.

That has been the main purview of the Board. It also has reviewed the specific drug safety postings that we have done to give us feedback on those, specific postings.

DR. GROSS: Any other questions? Yes, Terry.

DR. DAVIS: I was just curious about, does the Drug Safety Oversight Board write the patient information sheets and the information sheets for prescribers, or do the pharmaceutical companies write those? Who writes those?

DR. CUMMINS: Who writes the sheets? The sheets are written by FDA staff, and the Board has a small staff, and I have three fantastic staff that support the Board, and they work with other CDER staff to prepare the sheets.

They are developed across the Center, so the Office of New Drugs often starts it, because it is a new drug that they have primary responsibility for. The Office of Drug Safety weighs in. It is

really across-Center collaboration, and our staff facilitates and manages, and often plays a role in starting the ball rolling by drafting something that is then used, that it is then reviewed and commented on by other members of CDER.

DR. DAVIS: Is there a feedback loop that consumers or the target audience, the prescribers or the consumers, or both of them review these?

DR. CUMMINS: We don't have external review of the sheets by consumers. Again, to get back to your question about industry, industry is notified about a posting about 24 hours before a sheet is posted.

They do not have the opportunity to review and comment on the sheets prior to their posting, but we always welcome corrections, factual corrections especially, and those have happened, and we have changed them if there has been an error in the posting of the sheet, or there is a need to update the information, we have the capacity to do that very easily.

DR. DAVIS: The readability on them is

fine, and they are looking really good to me, but I just wondered if patients, if you have pilot tested them, patients, if they are helpful, if they are understandable, if they--

DR. CUMMINS: That's a great question. We are actually in the process of establishing a set of contracts to do research with our key target audiences, which are healthcare professionals and the public, patient groups and patients and patient caregivers.

So, those projects will start with a series of focus groups with those target audiences, and then that information that we glean from focus groups will be used to conduct a more general survey to get input about how we are doing and what we are doing.

DR. GROSS: Stephanie Crawford.

DR. CRAWFORD: Thank you. Good morning. I would also like to thank you for the overview, because most of what I knew about the Drug Safety Oversight Board was from the newspapers. This one was quite a bit more informative.

I want to comment to pick up on what Dr. Manasse had mentioned. In addition to looking perhaps at some efforts, either concomitantly, but preferably jointly, as this expands, in addition to biologics, perhaps looking at devices since so many drugs are integrated with the device systems now and it will be better if it was one system.

And just a quick question, could you please comment on the frequency of the meetings and the openness versus closed nature of the meetings?

DR. CUMMINS: Happy to. The meetings generally occur about every six weeks although a couple of times there has been a break in that six-week period when there hasn't been a need to meet, and the meetings are closed, and they are closed because we routinely discuss commercial confidential information that is pre-decisional and that we are required by law to keep private.

That is integral, that discussion is really integral to the work of the board, particularly because the focus is on internal management, how are we doing and how can we

facilitate and move along resolution or address kinks in that process.

DR. GROSS: Does CDER have an Executive Committee where all of the top managers meet?

DR. CUMMINS: I guess this is sort of--

DR. SELIGMAN: No, the answer to that question is yes, it has a senior management team that meets on a weekly basis.

DR. CUMMINS: That's right.

DR. GROSS: My concern is that the name Drug Safety Oversight Board may be giving the wrong impression. You have no public representatives. All of the people who are on the board are somehow beholden to the government. The so-called practicing physicians are still beholden to the government, and I think you need some independent people on that board even if you meet sotto voce without, you know, it going public.

But I think to give the confidence to the public, that you are meeting the needs that have been raised in the past year, I think you need a broader representation. I would also like to know

what is the relationship of the Drug Safety Oversight Board to this Advisory Committee. That's not clear.

I would think there should be a connection between the two, that we should be aware of the issues you are discussing, but I don't hear that.

DR. CUMMINS: Well, the board plays a different role than an advisory committee. The board focuses on content of communications and on processes, internal CDER processes, and again if you think of it as a convening of senior managers with additional input from federal employees external to CDER, it plays a central management role. It's a management tool to address processes.

It really is different than an advisory committee, and because we, at every meeting, discuss commercial confidential information, we really can't make it a public meeting. I appreciate everyone's interest in that.

Now, I can see the board, and it has discussed and anticipated routinely discussing and recommending advisory committees as part of the

process steps that are needed to fully evaluate, address, and deal with a complex safety issue, because keep in mind that the board tackles a small subset of the routine safety concerns that CDER handles every day.

But it plays a very different role than the role of this committee, for example.

DR. GROSS: Therefore, I think the name is misleading to the public. It is more of a referee committee, it is more of an executive type committee of CDER rather than really assuring safety in an open fashion.

Jackie.

DR. GARDNER: I would like to pursue Peter's question with a very specific example. Yesterday afternoon, after working all day, listening to questions of emerging interest in a safety issue related to ADHD drugs, that will probably--will need further study, I think we agreed, this committee strongly urged CDER to release information about the emerging risk, about what we do know and the fact that more study is

being conducted.

In fact, Dr. Laughren, I think even talked about these sheets. Can you tell me how that recommendation will proceed, will likely proceed from this committee's recommendation through to becoming an information sheet on process, and what is likely to be the amount of time it will take from yesterday's meeting until that happens, if, in fact, it is decided to do it?

DR. CUMMINS: What would happen is that Dr. Laughren would get in touch with myself and the Office of Drug Safety. We would meet, we would talk about the recommendation from the committee.

If our decision is to issue a sheet, we would draft it and move it through a clearance process, and that can happen really fairly quickly, within a week or two of the recommendation, or it can take longer.

A lot of what shapes that is deciding what data we want to put in and what analysis that we have done, and the data question can often be the piece that we need to resolve, so that it get it

right when we post it.

Does that answer your question?

DR. GARDNER: I guess I would just like to be reassured that we are talking about emerging risks as opposed to spending a really lot of time doing additional analyses and getting the words right, and so on, because our message yesterday was we want people to understand that this is a problem they need to be attending to, and we are going to keep setting it, you are going to keep setting it, as well.

But I would hate to see these kinds of communications get bogged down in making sure that--I don't want to say everything is correct, because, of course, it has to be correct--but I think unnecessary delays when we talking about emerging, that's a question I have.

DR. CUMMINS: I think that's a real challenge, trying to strike the right balance, and to provide appropriate level of data analysis and context when we are in the process of evaluating an emerging issue. It certainly has been a challenge

to the board.

It is one where there is a lot of--it's that area where there is honest disagreement about what the path forward is, and we have to really work through those issues, but there is, I want to reassure you, when we make a decision to issue a sheet, that process generally moves fairly quickly.

DR. GARDNER: And it's around that decision process I think that Peter's concern about this being strictly an internal process seems to not be moving us forward very fast or advances very quickly from what already was going on within the agency itself, therefore, the external interest.

DR. KWEDER: Susan, I can comment on that.

DR. CUMMINS: Oh, great.

DR. KWEDER: We share your concern. If you look at one of the challenges we have, I mean you all know what you go through for every meeting that you come to in terms of conflict of interest, discussions, paperwork filled out.

Anytime we have input from a party external to the government or even somebody in the

government, but mostly people who are external, they have to go through that. At any one of these Drug Safety Oversight Boards, we may discuss up to 20 products briefly, at least just present them, what is happening with them, where we think we are going, where the controversies are, where they may not be, so anyone who is participating in that would have to have conflict of interest clearance for every single one of those.

Sometimes, you know, because these meetings can only occur at most every four to six weeks, because they are a lot of work to prepare for, we are often in a situation where we have something that comes up two days before the meeting, because of information that comes before us that we didn't know about, but we feel the board needs to discuss.

Consequently, we have other things where the board, if you look at the list--so that's one issue of why it's a struggle to bring in people from outside the government, but it is something that we are continuing to evaluate.

I would say that the folks external to FDA, VA advisor, and our NIH advisor, are very, very helpful to us, and we have really put them to work on this Drug Safety Oversight Board.

The second issue is if you look at the list of sheets and communications that we have done, that Dr. Cummins shared, the vast majority of those have not been dealt with in advance by the Drug Safety Oversight Board, I just want to make sure that is clear.

The reason for that is timeliness. We are often, most of the time, in a situation where we don't feel like we should be waiting for the next board meeting in order to issue a communication.

In fact, one of the things that we bemoan is if you look at any major journals, if you just did a survey of the major journals in the country, on any given week, how many articles are there in a journal about some safety issue related to a new drug?

You know, a pharmacoepidemiology study or a clinical trial that shows some new safety issue.

These are things that we don't hear about in advance the vast majority of the time, so we are in a position of having to respond very quickly if something comes up that we think is worth us saying something about or putting forward a sheet about.

So, we keep Susan's staff very, very busy, trying to help us address some of those, and we don't feel like it's in many cases the right thing to do to wait for the Drug Safety Oversight Board to specifically weigh in on an issue.

We would then seek their input, making sure they have seen them, comments. In fact, we had some really good comments about one that we did on the long-acting beta agonists from one of the board members who pointed out something we did not address in it, and we had gone back and put something in about that.

But they are a supplement. They are a supplement to the work that our staff is continuing to do. Our goal is to make decisions in a timely way, and as you said, not twiddle our thumbs and back and forth.

We will go back after yesterday's meeting and convene kind of a post-meeting discussion and set forth a path forward that is quick and responsive.

DR. GROSS: Curt had a question.

DR. FURBERG: I also applaud the establishment of this internal Safety Board. It addresses some of the at least perceived weaknesses in the structure and organization, so I think that is a major step forward, but there are other areas that I think deserve attention that are not covered by the board, and I refer to one, the funding.

As I see it, in order to really address the safety issues in this country, we need to also look at FDA's authority, so what am I referring to?

Well, for example, in the labeling, when the recommendation is to add a black box warning, all that has to be approved by the manufacturer of a drug, and there are lengthy negotiations that are months, maybe up to a year before a black box warning is finalized and introduced. That is unacceptable.

I think the FDA should be given more authority in that setting for the labeling, and the black box warning is just one example of it.

The other one, equally disturbing, are all these committed post-marketing surveillance studies, that our commitments are made at hearings, and we know how many of them are outstanding.

I mean there are hundreds of them never committed, and many of them are just recommended to address safety issues, and it is really troubling, and the problem is that you, the agency, have no authority to really go after these companies who are violating their own commitments.

So, I am just wondering whether there are any efforts made to communicate I guess to Congress to address the issue about authority and how do we fix that problem.

DR. GROSS: Sean.

DR. CUMMINS: Could I just make one comment? Again, those are comments you might share, if you have ideas about it, with the Institute of Medicine Review Committee. They

actually have a specific web site where you can submit comments, and they are required to review those comments and respond to them.

DR. HENNESSY: I wanted to make a broader point about information that is submitted to the agency by sponsors that is considered to be proprietary. Drug safety and other decisions need to be made based on available information including both pre-marketing and post-marketing, and I think there is a tension between the proprietary interests of the sponsors and the public health interests.

In my mind, it is easy to say that the public health interests should trump the proprietary interests. By and large, these products have patent protection, and I think it does public health a disservice to have information outside of the scope of public view.

I just want to qualify that by saying that I am not referring to identifiable patient information.

DR. GROSS: Art was next and then Henri.

MR. LEVIN: A few things. One, I think I agree with Peter that the name of this board is extremely misleading I think to the public. This is really I would think an internal management committee, managing the Office of New Drugs and the Office of Drug Safety, adjudicating disputes and trying to bring in some outside experts within the government, but I don't think it's a drug safety oversight board.

It certainly isn't the National Transportation Safety Board, and I think that is what comes to my mind when we talk about an oversight safety board is an independent group of experts who look at disasters. In this case, it would be drug disasters, and do a forensic examination, and try to figure out how to avoid that in the future.

So, that is my model is the National Transportation Safety Board, and that is what I think a drug safety oversight board should be, so I would argue that the model is bad, the name is bad and misleading, number one.

Number two, I am confused when you are telling me you are talking about process issues and content of patient information sheets, where the proprietary tension comes in.

I agree with Sean, by the way, that I think it is overdone in terms of the public health. I don't understand when you are talking about a process issue, where that proprietary information would prohibit public participation, and at the very least, the public viewing of the work of the committee.

Maybe we can't participate or maybe experts can't participate because of the logical complexity of getting clearance, but why can't there be an audience, a sort of sunshine in the activities of this internal committee.

Lastly, what is perhaps most disappointing to me about the FDA's thinking on the future of drug safety, is that there is a whole flurry of activity out there around health information technology.

There is $50 million, you know, given to

Dr. Braylor and more money coming down the pike to develop health information technology, electronic medical records, and there is sort of this wild hope that with all this, we will push a button and get real-time drug safety surveillance, but anyone who knows his stuff knows unless you plan that in advance and build it into the systems, it is not going to happen.

So, we are always sort of thinking about this golden age around the corner where all of the burden of going through paper is going to disappear, and all of these problems will go away because we will have real-time information we can act on.

I don't see the FDA taking a leadership role in making sure that, as HIT whirls off into this sort of maelstrom of activity, that we are going to have built into that systems that give us real-time capability to observe both the good things and the bad things that are happening in the provision of drugs and devices, and other medical products to people.

DR. SELIGMAN: Art, in implementing HIT, there are a series of working groups at the federal level, and I am a member of one of those working groups that are actually focusing on public health surveillance and how to use these, you know, hopes for the future in terms of electronic medical records, and being able to meet the needs of not only the FDA, but many other federal agencies that have interest in timely and accurate and valuable surveillance data.

So, there is a working group process and structure, of which I, as well as other members of FDA, are part of.

DR. GROSS: Henri.

DR. MANASSE: This discussion stimulates in my mind a suggestion, namely, for a future agenda issue for this committee, and that is, drug information as an issue of safety, and let me tell you where I am coming from.

First of all, I question whether it should be a priority for the FDA given all of the concerns and issues in patient and drug safety, whether it

needs to get into the drug information business, if you will, to provide these leaflets, but we can discuss that for another day.

But research suggests that over 50 percent of the prescribing that goes on in this country is off-label prescribing, and it raises very interesting concerns, on what basis are these drugs being prescribed, what are the drug information resources that are available to stimulate that prescribing, how is that managed at all, significant issue.

Secondly, we have lots of vendors who are providing drug information. There is no regulatory scheme that says anything about what that content should contain, how it should be verified, what it should be linked to, et cetera, et cetera, and for those of you who might work with drug information, you know, it ranges from highly intensive clinical analysis, well documented, scientifically analyzed to plain garbage.

We have, as well, the Internet, and Lord knows what's on that Internet. Manufacturers have

drug information there, obviously guided by labeling requirements of the FDA, but lots of interesting anecdotes that comes onto the Internet, and fundamentally, what this all boils down to me is what can patients and health professionals reasonably rely on to make good clinical judgment and to manage patients well, what can patients rely on, how can patients be properly educated about the safety and risk and benefit of these drugs, make reasonable choices.

We heard impassioned pleas yesterday about that with respect to the stimulants and ADHD, and we have heard from Dr. Davis how complicated the production of drug information is with respect to patients understanding.

I think this is a very significant patient safety issue that we, as a committee, ought to deliberate, and I would suggest, Mr. Chairman, that perhaps at the next meeting, we have this as an agenda item.

DR. GROSS: Well, I probably won't be at the next meeting since I am off the committee, but

we will pass it on.

Terry.

DR. DAVIS: In following up on what Henri said, I want to point out the report of 2004, which said that 90 million Americans have trouble understanding and using health information, and that health information is unnecessarily complex. I think you all are moving in the right direction, but a couple things I want to point out.

One, just kind of gross measure is readability. You all are heading in the right ballpark, but these patient education handouts were written on a high school level. The average American is reading on an 8th grade level, and it's not just the reading level, but how user-friendly they are, and that is why you need consumers in there.

Also, as far as what patients can learn, they have less and less time with both the physician and the pharmacist, so these handouts are really important, and I think there should be some coordination between the handout and the sticker

labels, the primary label, which is the instruction, and the warning label.

Right now, for what I know, those warning labels are just random as everything. Different companies have different colors, different icons, different words, and there needs to be some more standardization, I think.

Also, are these handouts available in Spanish or any other languages?

DR. CUMMINS: We have not as yet undertaken a translation process. You know, to translate health information, you need to translate into the next language, and then have it translated back. We have had some discussions about undertaking translation, but not yet have we done that.

DR. GROSS: Annette.

DR. STEMHAGEN: My comment is about the level of evidence for issuing these emerging safety issues , and sort of a contrary point to Jackie's, which was things were discussed yesterday, and the question is when does it get

onto the emerging issues, but there have also been situations where a day or two before an advisory committee, an emerging issue was announced when the advisory committee was scheduled the next day or two to actually discuss it and look at evidence.

I just wonder how the timing of all that and the relationship with advisory committees comes in.

DR. GROSS: Sandy, did you have a comment?

DR. KWEDER: I wasn't going to answer Annette's question. I don't know if someone wanted to answer that. Susan?

DR. CUMMINS: I guess I am not aware of an issue that we have issued a sheet on for which there has been an advisory committee within a couple of days. Maybe you could give me an example.

DR. STEMHAGEN: I think, for instance, one of them was some of the immunomodulators and the issues related to cancer risks.

DR. CUMMINS: Topical immunosuppressants?

DR. STEMHAGEN: Yes.

DR. CUMMINS: There were two meetings on the topical immunosuppressants, one in October of 2003, and the next in--actually, it was February 15th, 2004. Was it 2004 or 2005? 2005, last year, that's right, the same day that Secretary Leavitt announced the Drug Safety Oversight Board.

Then, in March of 2005, we posted a Public Health Advisory on the topical immunosuppressants, and then have recently reached an agreement on labeling changes including the addition of a boxed warning about the potential cancer risk.

Now, there are postings put on the Internet about the meetings that include background information about the issues that the meetings are going to discuss, but those are different, under a different kind of venue for the advisory committee meeting postings than the sheets.

DR. STEMHAGEN: That is not what I was referring to, but perhaps I have the products wrong, so I will research that.

DR. KWEDER: I can respond to that. The background material for the February 2005 advisory

committee meeting on the topical calcineurin inhibitors included material that summarized the advisory committee discussion in 2003. That advisory committee in 2003 had recommended a black box.

So, there was also discussion in the FDA background materials recounting that and some of our internal work that had been going on toward that in the interim between 2003 and 2005.

So, there was information released in advance of the advisory committee meeting, but it was because the discussions about a black box had been underway during that entire two-year period.

What I wanted to say, Dr. Gross, was I wanted to just address Dr. Hennessy's and Mr. Levin's comments about proprietary information. Dr. Hennessy, you mentioned that you think that public health and safety should trump--maybe that wasn't your word--should trump proprietary interests.

I think we all have frustrations about what we can say and when, and patents aren't the

only issue. There are many legal types--the term that we confront most often is commercial confidential information.

It is a really delicate balance for us. In extreme circumstances, we are able to get rulings that sometimes the public health does override, but it is very complex. Those are regulations that have been in place, regulations and laws that have been in place for a very long time, and we work with them as best we can.

I just want to reassure you that it is not because the FDA wants to withhold information.

DR. GROSS: Sean.

DR. HENNESSY: I realize that, and my comment was to get on record that I think that the regulations under which you work should be changed.

DR. GROSS: Any other comments? If not, I would just like to summarize my thoughts.

I think the FDA people here and the FDA in general is an incredibly competent organization. You really do a fabulous job, and I think you are setting yourself up for failure with this oversight

board. In this age of transparency, you decide to have a committee that is responsible, according to its name, for overall safety, and yet it meets in private.

You don't have public representatives. You are under enormous pressure from the public, from the government, from industry. I don't envy you at all. But I think this process of oversight has to be more transparent.

Jackie.

DR. GARDNER: Sorry, I hate to speak after your summary.

DR. GROSS: Go for it.

DR. GARDNER: Well, I just wondered whether we, as a committee, might take some positive action toward communicating with the IOM Committee, as has been suggested by FDA staff twice this morning, and both you and Curt, and I think Art, had particular recommendations having to do with both resources and authority of FDA to pursue some of the things that are frustrating to them and that frustrate us.

They have said tell the IOM, which I think is a step up from write your congressman, which is what we usually are asked to do.

So, could we, as a committee, take some action with motions, which I would defer to Curt to make probably, he would be more eloquent than I, and to the point, that we could vote on it, and then actively convey them to IOM, if that is what we think is the best way to do it?

DR. SELIGMAN: I have just been tapped on the shoulder by the IOM project director, who is here with us today. Her name is Kathleen Stratton. I have all her contact information here and would be happy to provide it to you, but I certainly agree with you that I think this is certainly the right moment given that we are putting a lot of pressure on the IOM to give us a report this calendar year.

As I said earlier, the time is ripe for such input on many of the concerns and issues that you all have raised in this morning's discussion, including the point that you made, Dr. Gross, about

the way we manage drug safety internally within the FDA.

This was also a charge to the IOM Committee, as well, to look at, and, indeed, if there are concerns about either the title or the way we manage internally some of these concerns, I think again the IOM would be I think the right venue to raise those concerns and recommendations.

DR. GROSS: Thank you. Our intentions are to make you look squeaky clean. They are all very good intentions, so I hope you take it that way. Thank you.

Believe it or not, after all that discussion, we are still early on the agenda, but we will take a break now and reconvene at 10:30 rather than at 10:45.

[Break.]

DR. GROSS: Well, thank you all for coming back.

The next speaker is Dr. Sharon Hertz, who will give us an update on the NSAID labeling and data review.

An Update on NSAID Labeling and Data Review

DR. HERTZ: Thank you for the invitation to provide this update today. I am with the Division of Anesthesia, Analgesia, and Rheumatology Drug Products, still learning the new name.

[Slide.]

I am going to review for the committee today just what we have done since the information about cardiovascular risk was discussed last year.

Here, I have the beginning of the timeline that shows the events that started September of 2004, where we were first informed about a cardiovascular signal for rofecoxib when compared to placebo in the APPROVe study, followed by Merck's withdrawal of Vioxx from marketing.

We then later learned that there was a cardiovascular signal for celecoxib versus placebo, and another trial that was halted, the ADAPT trial.

[Slide.]

We convened an advisory committee, a joint committee, that included the DSaRM and the Arthritis Advisory Committees, and discussed the

safety information available at that time.

In April of last year, the FDA issued a memo that described the cardiovascular risk associated with NSAIDs, and the following day, we issued an information request letter asking sponsors to review information on their NSAIDs with regard to any possible cardiovascular signals for products that weren't specifically discussed at the meeting.

We also issued a labeling supplement request letter to update the NSAID labeling, which is to some extent template based.

[Slide.]

The specifics of the labeling changes that we requested started with a new boxed warning to describe three points. The cardiovascular risk that is associated based on the available information, we think that this may be true for all of the NSAIDs regardless of selectivity.

[Slide.]

We, based on information available, have asked for a contraindication for the treatment of

perioperative pain in the setting of CABG.

[Slide.]

We also raised the warning that has been known for gastrointestinal risk to the level of the box.

[Slide.]

There are additional elements of the labeling that were also amended. We have put some caution type statements in indications and usage to consider the potential benefits, as well as the risks, use the lowest dose for the shortest period of time compatible with treatment goals.

[Slide.]

The contraindication was also added to the section on Contraindications, specifically, for use in the perioperative CABG setting.

[Slide.]

We have created some new warnings for the label. One is describing the cardiovascular risk in greater detail. I don't have all of the new language here on slides, because it is a lot, and the idea is just to give you an idea of where the

labeling went.

[Slide.]

So, the first warning is that we have data from several products that describe a cardiovascular risk specifically for cardiovascular thrombotic events, which can be fatal.

[Slide.]

We think that both COX-2 selective and nonselective products may have a similar risk and that patients who already have risk factors for cardiovascular disease may be at greater risk.

Again, the admonition to use the lowest dose for the shortest period that is compatible with treatment.

[Slide.]

We don't know that based on the available information, the use of aspirin adequately mitigates the cardiovascular risk. We do know that aspirin increases the GI risk associated with concomitant use with NSAIDs, so that is now in the Warning section, as well as the CABG-associated risk.

[Slide.]

We have other elements in the labeling - new warnings about hypertension, CHF and edema. Renal effects were upgraded from precautions, advanced renal disease, anaphylactoid reactions, skin reactions, serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, as well as a warning about use in late pregnancy because of premature closure of the ductus arteriosus, as well as the existing warning, which was fine-tuned a little bit, about the GI effects.

[Slide.]

The Information for Patients section was improved to reflect these warnings, so there is this cardiovascular risk, GI, skin, the CHF risk, also, just to alert patients for signs of hepatotoxicity, anaphylaxis, and to avoid in late pregnancy.

[Slide.]

Dosing and administration was also given some additional statements.

[Slide.]

The information request letter that went out to all of the sponsors holding applications for NSAIDs asked for a review of clinical trial data, and this data goes back decades, because it included all of the currently marketed NSAIDs.

We asked them to review data from studies that were at least one month in duration and which were controlled in some way - placebo, dose-response, or active control.

[Slide.]

This was important because the criteria for studies that supported approval in the past differed from what would currently be requested, so we broadened the categories to include all of these different elements, different types of study design.

We asked for, from these studies, any adverse event reporting for cardiovascular death, MI, stroke, hospitalization for CHF. We asked for the definitions of the events to the extent they were available, and also relevant baseline

characteristics - pre-existing hypertension, heart disease, and so on.

[Slide.]

Although we had had a fairly extensive review of epidemiologic and observational studies at the advisory committee, we also put that in the information letter just to make sure that we had the available information, and we didn't really receive any new information in this area with the results from the information request.

We asked sponsors to look at what information they had about blood pressure changes and to submit that, as well.

[Slide.]

To the extent possible, we wanted to look at concomitant use of aspirin and if there had been any subsequent information since filing about the lowest effective dose, anything new that had come to light.

[Slide.]

Well, we got a lot of information submitted, and it was a pretty big task to start

looking at it. So, we organized a working group with representatives from the Office of New Drugs, the Office of Drug Safety, Office of Nonprescription Drugs, and Office of Biostatistics to embark on this review.

The information that was submitted was reviewed, it was re-analyzed in an attempt to try and look at it in different ways.

[Slide.]

I am going to take you through one of the better sets of information that we got from one particular sponsor of several NSAIDs, and not that I want to frustrate anybody in the room, but I have left off names or individual identifications because we are not in the kind of setting in which we are really prepared for the sponsors to speak and give fair balance.

This is just to give you an idea of what kind of information came in and what we thought we could do with that information. As I go through, I think you will see that this may be sufficient for the purpose of an update today.

[Slide.]

So, one particular company performed a variety of meta-analyses or pooled analyses for their products, and they looked at placebo- and active-controlled studies, basically following the type of requests that were in the information letter, information request letter.

I have two slides showing four different NSAIDs for which information was submitted, and just to give you an idea of what we were looking at when this information came in.

[Slide.]

For these two products on this slide, we can see that we have a number of studies, and we have some sample sizes that are starting to reach reasonable sizes for this type of analysis, but overall, the number of patients in these individual studies was small because they were predominantly efficacy studies.

The open-label extension studies that provide a lot of the safety information really weren't suited for any kind of comparative analysis

of cardiovascular risk.

You can see we got placebo-controlled studies, active-controlled studies with other NSAIDs, as well as studies using aspirin as a therapeutic agent, as an active control.

The reporting of cardiovascular events was low. I will show you the next slide, which is pretty much similar.

[Slide.]

So, these are four representative NSAIDs to give you an idea of the kind of information that is available in the older records.

[Slide.]

When we looked at all of this information, we dug into it, we asked for some clarifications. We looked at all of the sponsors who submitted information, and we came to some conclusions, and that is, the data available through this information request letter was not able to support evidence of the presence or absence of an association between these older NSAIDs, and some of the newer ones even, and cardiovascular adverse

events.

The limitations were that the sample sizes were generally small, even with pooling. The studies were very short duration. They were four, six, eight weeks. We had some up to 24, 25 weeks.

There was a tremendous amount of heterogeneity and variability in design, populations from trial to trial, and it is important to note that these trials really weren't intended to look at this as an outcome.

These were efficacy studies for the most part. There really wasn't a question about cardiovascular risk associated with nonselective NSAIDs at the time these products were under evaluation.

So, we can't really add to our current knowledge of cardiovascular risk outside of the products that already have these large studies that were discussed last year.

But the important thing is that we did, to the extent possible, look at the information to see what it could possibly inform.

[Slide.]

The nonprescription NSAIDs, we also looked at those. A lot of the information that was submitted was from the original Rx applications, as well as the over-the-counter switch studies, and we had the same issues.

The original studies for the Rx products were small, short, and there were few events. There were no adjudication processes. It was just not suitable for this type of analysis. Of course, the OTC studies themselves were generally less than a month in duration.

[Slide.]

So, just to let you know where we are now, we have just about completed all the NSAID label updates. There is a couple of unusual, not standard NSAIDs, that we are just finalizing some of the last details. So, that has been completed.

When we look back at the experience from the products that did show signals, and the studies that were required in order to get those signals, the large outcome studies, we have decided that new

NSAIDs under development should perform medical outcome studies to evaluate cardiovascular outcomes pre-approval.

Just to give you an update, as one of the other elements from the advisory committee meeting was that there would be an additional outcome study for celecoxib.

I can't provide much detail at this point in time, but I can just say that we have not yet come to agreement with the sponsor over a trial design, and we have discussed some concerns with the proposed protocol with the sponsor.

So, if you have any questions.

Questions and Answers

DR. GROSS: Thank you, Dr. Hertz. My compliments to you for your thoroughness, balance, and actions taken by the FDA.

Dr. Furberg.

DR. FURBERG: I am sensing a contradiction. We have the conclusion on page 13, the slide saying that the data from the trials do not support the presence or absence of an

association with cardiovascular events, emphasizes small trials, short duration, few events, heterogeneity, basically, you can't conclude very much, and on that information, you decided to go ahead with a boxed warning.

So, the scientific justification for that is weak when it comes to the traditional NSAIDs. For the COX-2s, we have individual trials confirming harmful effect, but for the others, I think the documentation is very weak, and I just wonder why you took that action.

Yesterday, we had the discussion about the drugs for attention disorders. We were told that the black box warning wouldn't be appropriate because we don't have enough information.

What is the consistency here? Why do we have inconsistency?

DR. HERTZ: Well, I think that there is not quite so much inconsistency. This data that came in as a result of the information request doesn't support a finding, so we can't attribute individual risk or identify risk associated with

some of these older products.

But the larger outcome studies, several of them did have nonselective NSAID comparators, and when the analysis was done that reviewed those studies that had active comparators, it was felt that there really wasn't any clear difference or consistent difference between the nonselective and selective NSAIDs.

So, the statements that went out last April, and the labeling changes that went out, reflected the analysis of those large outcome studies, and the concern that based on the available information, there does not appear to be the ability to distinguish risk between the different types of NSAIDs or even to rank-order the risk among those studies, those products that had studies.

DR. FURBERG: I don't think you have much power to make that claim. I mean you are dealing with small numbers. It still can be a fairly substantial difference between them, and that somehow is lost.

DR. HERTZ: Well, I hope that some of that can start to be addressed further as we get additional studies, so we are looking to the next study, perhaps the Celebrex study, to help add some additional information.

There is always the opportunity for other products to come in and show us that there is no risk associated with them, but in the absence of anything more than what we currently have, that the outcome studies, as they were reviewed, that data was considered, we felt that this supported the most appropriate response for the available information that we had at the time.

DR. GROSS: Arthur.

MR. LEVIN: At the February meeting, we had presentations on two product in the pipeline. What has happened with those new products, have they moved forward? Is there more study involved? I am just curious where they are. I don't remember the names of the two drugs, but there were two drugs that we had presentations on that were pre-approval in the pipeline.

DR. HERTZ: Right. I don't have any new information that I can report on those.

DR. GROSS: Any other comments or questions?

DR. MEYER: I am Dr. Robert Meyer. I am the Director of the Office of Drug Evaluation II, under which DAARP, and I am not going to even try to say the name, resides.

I just wanted to be clear in response to Dr. Furberg's question, that the timing of this was that the black box decision was made on the basis of the large outcomes trials, which included NSAIDs as comparators.

This data request and analysis was sort of a secondary check on our part to see whether there was something more that could be made of the existing clinical trials databases that would further inform or refine our actions that we have already taken.

The conclusion is, despite I think a very good effort by a multidisciplinary team at the FDA, is that these data do not further inform our

decision.

DR. GROSS: Thank you for that clarification.

Hearing no other comments, Dr. Jill Lindstrom will introduce, give us an update on the isotretinoin risk management program and the new approaches.

Introduction to Isotretinoin Risk Management Program

DR. LINDSTROM: Good morning. Today, we are going to inform you about changes that have been implemented to reduce the risk of fetal exposure to isotretinoin.

[Slide.]

As you know, isotretinoin is indicated for the treatment of severe recalcitrant nodular acne. It is the only drug moiety approved for this indication, which is devastating and often permanently disfiguring.

Isotretinoin is also a potent human teratogen and over its 24-year marketing history, a series of progressively more rigorous risk

management tools have been implemented to try to mitigate this risk.

When I last stood before you in February of 2004, the sponsors and the agency presented information to this committee about the impact of the sticker risk management program known for the innovator by the acronym SMART, largely in part because the number of pregnancies reported to the agency in the year following the implementation of the sticker program, were not substantially different than the number of pregnancies that had been reported in the year preceding implementation of that program.

[Slide.]

This committee, in combination with the Dermatologic Advisory Committee, advised that the sticker risk management program be revised.

Additionally, because there were multiple programs, although in content quite similar in name and logo, and in terms of material, they were different for the innovator and the generic companies going by the various names - SMART,

SPIRIT, IMPART, and ALERT, you advised that these multiple programs be consolidated into a single revised program with one set of materials, one name, and one logo.

[Slide.]

You recommended that this consolidated revised program include registration of all patients, both men and women, registration of prescribers and pharmacies, and a tight link between pregnancy testing and dispensing of the drug, as well as implementation of a pregnancy registry to assess the root cause for any fetal exposure that might occur.

Since we received these recommendations from you, both the agency and the sponsors have been working vigorously to implement them.

[Slide.]

On the part of the agency, we established a working group with broad representation from across the Center including involvement of representatives from the Office of New Drugs, the Office of Generic Drugs, the Office of Drug Safety,

the Office of Compliance, Pregnancy and Lactation Team, as well as representatives from the Division of Drug Marketing and Communication later in the process.

We met together internally and met with the sponsors, as well. Internally, we drafted the white paper, which was included in your background package, and in that white paper, we had articulated our conceptual framework for a risk management program that would incorporate your recommendations.

This white paper was provided to the sponsors in July of 2004, and by September of 2004, they returned to us with a presentation of a conceptual framework for the program that they were developing.

By December of 1004, they presented us with a submission timeline, and from that point through June of 2005, they submitted components, detailed components of their program for agency feedback and comment, and their labeling supplement, which detailed the complete program,

was submitted to the agency on June 24th, 2005.

[Slide.]

This underwent accelerated review by the agency and was approved under Subpart H on August 12th, 2005.

The following month, registration began for wholesalers and pharmacies, and patient enrollment was begun on December 30th, 2005, and we anticipate the transition will be complete on March 1st, 2006.

[Slide.]

The iPLEDGE program involved participation by all of the stakeholders involved with isotretinoin from wholesalers to pharmacies to prescribers and patients. They interact with a technology-based, performance-linked access system to ensure that only qualified patients receive the drug.

Now, in a few minutes, the sponsors are going to describe this program in much more detail, but before they do, I want to point out just a few unique aspects of the program.

First, although there are other performance-linked access risk management systems in place, this is the first that has been implemented for a widely prescribed drug.

Second, this is the first time that the innovator and generic firms, essentially marketplace competitors, have come together and cooperated in the interest of public health to develop a single consolidated risk immunization action plan of this magnitude.

Finally, we are implementing this risk management program iPLEDGE in a multi-source environment. The drug, as has already been mentioned, has been marketed for many years, it is widely prescribed, and as such, in our free market system, normal and complex distribution channels are in place to ensure delivery.

The legitimate interests of these parties, the distributors, up to approximately 200 wholesalers and distributors, perhaps 55,000 pharmacies, as well as all of the prescribers and patients, have needed to be taken into account.

[Slide.]

While these unique aspects have represented unique challenges for us, I think they also represent unique achievements of this really unprecedented program.

[Slide.]

Now, although much has been accomplished, there is still work to be done. Both the agency and the sponsors are aware that program refinements may need to be made.

Additionally, we anticipate and look forward to having a public discussion about the metrics of the program, what measures will we look at most closely, how will we define success, what comparisons in terms of time will we make, and while we do look forward to a public discussion of metrics and these issues, it is not the focus of today's presentations or discussions, which are intended to be informational in nature.

I will be available for questions afterwards, but I think it probably would make the most sense now to invite the sponsors to come up

and present the details of the iPLEDGE program.

DR. GROSS: Dr. Susan Shiff will talk about the risk management program for pregnancy.

iPLEDGE Isotretinoin Pregnancy Risk Management Program

DR. ACKERMANN SHIFF: Good morning. My name is Susan Ackermann Shiff. I am the Global Head of Risk Management for Hoffmann-La Roche. We appreciate the opportunity to meet with the FDA and the committee to give you some insights into iPLEDGE, or the pregnancy risk management program for isotretinoin.

It is a product of a collaboration unprecedented in nature among five companies - Hoffmann-La Roche, Mylan/Genpharm, Ranbaxy, and Barr, and our vendor partner Covance.

[Slide.]

Today, we would like to describe for you the program's development, the update on the program, the structure of the program, and our implementation.

This presentation is divided into three

sections. I will give you an overview of the program, also, how we have evolved from SMART to iPLEDGE. Christine Mundkur, from Barr Laboratories, will describe for you a little bit about the development process of iPLEDGE, and then finally, James Shamp will describe the program.

[Slide.]

The last decade has had the same public health goals, that we want to ensure that no female patient becomes pregnant before starting isotretinoin, and no female patient becomes pregnant while on the product.

[Slide.]

Based on the public health goals and our discussions from SMART, and what we know about risk management from 20 years on the product, the system of iPLEDGE is a verification of checks and balances, and documentation that requires:

Mandatory registration of all members of the system, prescribers, patients, pharmacies, and wholesalers;

Mandatory monthly laboratory pregnancy

testing that is verified by the prescriber and by the pharmacist;

Mandatory interactive educational component on a monthly basis;

All that to be authorized before the patient can actually get the dispensed product.

[Slide.]

I would like to briefly describe for you the evolution of risk management and how we actually came to iPLEDGE and the data we used to develop the system.

[Slide.]

As everybody recalls, we have had a long history of risk management on isotretinoin. The product was approved in 1982, and Dr. Thiboutot said quite eloquently the use of isotretinoin is for severe recalcitrant nodular acne, for patients who are unresponsive to systemic antibiotics, and we should remind ourselves of the painful and disfiguring condition, particularly the scarring and permanent scarring that could be in place if the patient does not use a product.

There is also no other product available that can resolve these lesions.

We also know from Dr. Thiboutot that teratogenicity was known about the product since its launch in 1982. We have worked with the FDA to develop a variety of different pregnancy prevention programs.

The first one of its kind was in 1988. It included a voluntary survey, educational materials, and more important, pregnancy testing requirements and contraceptive requirements.

We have had frequent enhancements through to 2002 to the SMART program, the system to manage Accutane-related teratogenicity.

This incorporated the components from the Pregnancy Prevention Program in addition to the yellow sticker that verified the negative pregnancy test.

[Slide.]

In 2004, we were here with our generic colleagues, and we provided you with the first year of SMART results. In addition, the sponsors in

total proposed a single enhanced pregnancy risk management system that included registration of prescribers, pharmacists, and patients, a pregnancy registry, and educational components.

At that time, the joint committee agreed with our proposal and provided some insights into enhancements.

[Slide.]

I would like to now just take a few minutes to describe to you what we presented at the 2004 advisory committee, more importantly, the data that we used from SMART to inform iPLEDGE.

As you recall, SMART had prescriber, patient, and pharmacy requirements, and briefly, the prescriber requirements included reading and understanding the risk management program, signing a Letter of Understanding, and then getting the yellow stickers.

Again, the yellow sticker was a verifiable link between the negative pregnancy test and the dispensing of the product.

Pharmacists were checked to ensure that

that yellow sticker was on the prescription. They would dispense no more than a 30-day supply within the 7 days of the negative pregnancy test or the 7-day window. No telephone refills, computerized prescriptions were allowed.

[Slide.]

Finally, the patients had to visit their prescriber on a monthly basis, have had a negative pregnancy test, committed to using two safe and effective forms of contraception, and sign their two informed consents, both the all patient and the pregnancy, and be informed of the purpose of the Accutane and isotretinoin surveys.

[Slide.]

We evaluated year one of SMART using three different data sources, the Prescription Compliance Survey, the SMART revised Accutane Survey, and then actual case reports.

[Slide.]

I would like to briefly review the data we had from the first year of SMART.

First, the Prescription Compliance Survey,

and that was the audit of filled prescriptions at a sample of pharmacies. We found that the stickers were working well, 97 percent were utilized, 96 percent were completed correctly. The mechanics worked well, but the sticker did not represent a negative pregnancy test.

[Slide.]

From the Accutane Survey or the Epidemiologic Survey that has been in place since 1989, and developed by the Sloan Epidemiology Unit of the Boston University School of Public Health, it asked various issues related to risk management including contraception use, sexual practices, and important components of adherence to the program.

We were able to increase the enrollment rate from 17 to 28 percent, but we didn't reach our 60 percent metric, so women weren't participating in the survey. More importantly, however, 9 percent of females who recalled the yellow sticker did not recall having had a pregnancy test prior to the initiation of therapy.

While they understood the need to avoid

pregnancy, they certainly did not understand the need to practice contraception or get their pregnancy tests.

[Slide.]

Finally, when we looked at the absolute numbers, as Dr. Lindstrom mentioned before, pre-SMART, SMART, and again, the calendar year we used is April 1st to March 31st for pre-SMART year, and then April 1st of 2002 through March 31st, 2003 for SMART Year 1, the absolute numbers increased from 150 to 183.

We were successful in reducing the percentage of women who were pregnant at the physician's office prior to the initiation of therapy, and in reducing the percentage of women who got pregnant while on therapy, but there was a large number of unknowns that could potentially skew that data.

[Slide.]

So, what did all this mean? We had 20-plus years of history and risk management on the product. We have data from SMART Year 1, and we

certainly realized, along with our generic colleagues, that we had to improve SMART, which now is ultimately iPLEDGE.

The further tightening of the existing link between the negative pregnancy tests and the dispensing of the product was an absolute must. Reinforcement in education was another must.

We realized that a single risk management program for the molecule would reduce confusion. The limited participation in the voluntary survey had to be considered, and the centralized pregnancy reporting system that allowed us to do root cause analyses on each of the pregnancies would help improve subsequent programs.

[Slide.]

The feedback we received from the joint advisory committee was very consistent. They also suggested full registration of all healthcare professionals, comprehensive testing of the educational materials, so that they would be useful, mandatory patient follow-up, and then the launch of the program should not be delayed by a

pilot or any cost analysis.

[Slide.]

Specifically, iPLEDGE used all these enhancements together. The tightened pregnancy testing link, now we have a laboratory-confirmed pregnancy test. It must be entered into the system by the physician and then confirmed by the prescriber.

Reinforcement of contraceptive use and the importance to continually remind women to use their contraceptive correctly was an absolute must.

Now, patient and prescriber entries into the system must match their primary form. In addition, patients must answer monthly questions related to their contraceptive choices and several components of risk management.

The single risk management program ensures reduced confusion among all key players in the system.

[Slide.]

Limited participation in the Accutane and isotretinoin surveys. Now, we have patients

answering monthly questions into the system, again confirming their commitment and their cooperation with the risk management program.

Finally, a centralized pregnancy reporting system allows us to do root cause analyses on all of the pregnancies that come into the system, and it requires vis-a-vis the USPI that prescribers must report all isotretinoin-exposed pregnancies.

Finally, we have an enhanced lost to follow-up plan to follow women who are pregnant, to get the information necessary to improve future programs.

[Slide.]

What we have come to after 20 years of experience on the project, after SMART Year 1 data, after consultation with the FDA, the advisory committees, and various stakeholders is the iPLEDGE program.

The centralized pregnancy risk management system with mandatory registration of wholesalers, prescribers, pharmacies, and patients, enhanced education, a pregnancy registry, and ongoing

program improvement, we hope to further reduce fetal exposure.

I would like to now turn it over to Christine Mundkur, who will talk briefly about the development process of iPLEDGE.

MS. MUNDKUR: Thank you, Susan. Good morning.

I am Christine Mundkur with Barr Laboratories. I am the Senior Vice President of Quality and Regulatory Counsel.

[Slide.]

iPLEDGE builds on the pregnancy prevention programs that Susan previously described. We took those learnings and continued to develop the iPLEDGE program. Today, I will provide you an overview of this program and the development timelines that we went through.

As you have heard, iPLEDGE is the first of its kind in scope and complexity, where multiple manufacturers, competing manufacturers collaborated with Covance, our vendor, with FDA, and the key stakeholders to develop one comprehensive risk

management program for an existing product that goes through normal distribution channels.

[Slide.]

The purpose of this slide is to really demonstrate the unprecedented scope of the development of the iPLEDGE program. The five competitive manufacturers came together after the 2004 advisory committee and determined that we needed to develop one central program.

Because of the complexity of the requirements and due to the diversity and large number of our stakeholders, Covance needed to design and develop one novel computer-based program.

No other risk management program has the volume of users interacting with it. Specifically, for iPLEDGE, the annual registry participation may be 298 wholesalers, 36,000 prescribers, 55,000 retail pharmacies, and potentially 200,000 patients.

[Slide.]

The development of iPLEDGE has been a

series of interdependent and complex elements that the manufacturers have been working on since the advisory committee in 2004 to move the development process along in a timely manner.

We immediately started working on the vendor selection process, ultimately deciding on Covance in August of 2004. In parallel, we began discussions with the agency to further define and develop the requirements and the elements of the program.

This dialogue has continued throughout the development, the approval, and the transitional phases of the iPLEDGE program. It included multiple discussions and submissions with the agency including five different division groups, which resulted ultimately in the submission of the labeling supplement in June of 2005, and its ultimate approval is in August of 2005.

[Slide.]

Early in the development process, the Celgene patents were raised as a potential issue. The manufacturers together reached a resolution

with Celgene in coming to a licensing agreement.

The manufacturers also understand the importance of communicating and interacting with the various stakeholders including the development of our Scientific Advisory Board. We began these efforts in November of 2004 and starting to communicate with all of our various stakeholders.

Ultimately, the past several months have been focused on the transition from the SMART programs to the iPLEDGE program. Specifically, we have been focusing on the education, the registration, and the activation of the key stakeholders.

Some of the key milestones include actual sending out the registration materials to the wholesalers, prescribers, and pharmacies in September of 2005. We began patient registration the end of December, and we have the mandatory registration and activation of all stakeholders for March 1st.

[Slide.]

Stakeholders are very important to the

success of the iPLEDGE program. Therefore, the sponsors created a Scientific Advisory Board for iPLEDGE in order to obtain feedback from them.

The stakeholders include representatives for all key areas - the healthcare providers, the pharmacies, wholesalers, researchers, and patients.

We presented the framework and key concepts during the development of the program, however, it wasn't until the stakeholders had an opportunity to really see the overall program and to actually have an opportunity to see how it would work under real life practice did we really get the majority of the feedback back.

We continuously ask from our stakeholders for feedback, so that we can assess it, review it, and implement where we can quick fixes and otherwise also looking for continued enhancements to the program.

[Slide.]

One consistent message back from our stakeholders has been the need for a transition time. They needed the time to go from the existing

SMART and SMART-like risk management programs over to the iPLEDGE program.

That need for time was, one, to educate themselves, to educate their staff, also, to look at how these processes, the new processes would be introduced into their existing business practices, as well as to make sure that the staff would understand and be able to participate in the iPLEDGE program.

We began the transition period for the patients and doctors on January 1st.

That is currently where we are as far as from the development program is during the transition phase.

In conclusion, I would like to say that this collaborative effort between all of the sponsors and the five different divisions of the agency, and through our Scientific Advisory Board has produced iPLEDGE, which in itself is a comprehensive, multifaceted risk management program that will further enhance the pregnancy prevention goals associated with isotretinoin.

Thank you.

I would like to now introduce James Shamp, from Covance, and he will be discussing the iPLEDGE program.

MR. SHAMP: Good morning.

[Slide.]

I am Jim Shamp, a director with Covance, and I will be presenting a system overview to you this morning, as well as a status update.

[Slide.]

This first slide shows all of the stakeholders participating in iPLEDGE, starting on the left and going clockwise with the manufacturers, the wholesalers, pharmacies, patients, and prescribers.

This picture also shows the product flow from the manufacturers, through the wholesalers, to the pharmacies and eventually dispensed to the patient.

Additionally, you can see the interfaces between the participants and iPLEDGE with the arrows going in to iPLEDGE, as well as the

interactions between each of the stakeholders, for instance, the prescriber with the patients.

We register all patients in iPLEDGE. We do this to create a baseline data point of all patients participating in iPLEDGE, as well as to provide data for prescription dispensed through iPLEDGE.

[Slide.]

I will start with walking you through the process required to qualify a female patient of child-bearing potential for isotretinoin, and the next several slides will build on this process.

It starts with a prescriber identifying a patient that should receive isotretinoin.

[Slide.]

At the initial registration visit, the prescriber first determines if this patient is child-bearing potential, and if so, a screening pregnancy test is required, and this test must be negative before the registration occurs.

Next, the prescriber educates the patient and then registers the patient in iPLEDGE, entering

patient demographics, as well as a unique patient ID for this patient.

Once this registration is complete, the system then enforces a 30-day wait before any other activity can occur for this patient. The reason for this is to enforce the requirement that this patient must be on two forms of contraception for 30 days prior to receiving her first prescription for isotretinoin.

Additionally, in this time period, the patient must receive contraception counseling. This can be performed either in the prescriber's office or the prescriber can refer this patient to another healthcare provider for this contraception counseling, in which case iPLEDGE will pay for that visit.

[Slide.]

After 30 days have gone by, the patient can return to the prescriber's office, or the prescriber now confirms this patient in the system. It starts with the prescriber entering two forms of contraception that this patient has chosen to use.

The prescriber additionally educates the patient again, providing counseling, orders a laboratory-conducted pregnancy test, provides the patient with the prescription, and after completion of this confirmation in the system, this begins the 7-day window that the prescription must be filled.

[Slide.]

Three things have to occur in the 7-day window. First, the patient must have the laboratory-conducted pregnancy test performed. Additionally, the patient must interact with the education and risk management component of the system. This is where she enters her two choices of contraception, and the primary choice that she enters must match with the primary choice that the prescriber entered or else this patient does not qualify to receive isotretinoin.

[Slide.]

After she enters her choices for contraception, the patient then answers a series of questions about the program, about the requirements, about birth defects, and about

contraception.

After completing that, the prescriber still must enter the pregnancy results. When the prescriber enters the pregnancy results, if the results are positive, this prevents this prescription from being filled and prevents the patient from getting isotretinoin.

If it is negative, this patient is now qualified to receive this prescription. The patient can then take her prescription to the pharmacy, where the pharmacist must authorize the prescription fill through iPLEDGE, and this can be performed either on the web or over the phone.

The system, as part of the authorization, confirms all the requirements have been met for this patient this month, including that the prescriber is registered and activated, the patient is registered, the patient has been confirmed in the system, the patient has answered her monthly questions, and a negative pregnancy test exists for this month for this patient.

If the system determines those

requirements have been satisfied, the pharmacist is then required to enter product information into the system, and the system then provides a risk management authorization number back to the pharmacist, and the pharmacist is required to write this number on the prescription, which then provides an audit trail of that prescription to the authorization in the system.

Additionally, the system also provides a do not dispense to after date to the pharmacist, and the pharmacist writes this on the prescription bag sticker that iPLEDGE provides to the pharmacist. This is the date that the prescription must be dispensed to the patient by. If the patient comes in to pick up the prescription after this date, the pharmacist cannot dispense to the patient.

[Slide.]

So, now the patient receives her 30-day supply of isotretinoin for this month, and then must wait at least 23 days before she can start this process over to receive another prescription,

thereby enforcing a maximum 30-day supply for any one month for a patient.

It is these activities and these interfaces that provide the verifiable link in iPLEDGE to these requirements.

[Slide.]

Upon completion of therapy, the female patient of child-bearing potential has some additional requirements, which are she must obtain another monthly laboratory pregnancy test upon completion of therapy, she must continue using her two forms of contraception for another 30 days, and she must have an additional laboratory pregnancy test 30 days after completion of therapy.

The prescriber is required to enter the results of both of these pregnancy tests into the system, and this is to ensure that the patient is not pregnant the 30 days after therapy.

[Slide.]

As you can see, all of these links are in the system. Because of that, we are able to provide a determination if an expected activity has

not occurred for a patient. For example, if the last pregnancy test 30 days after therapy does not occur, the system recognizes this, and then marks that patient as lost to follow-up.

When iPLEDGE recognizes this, several things happen. We first try to attempt to contact the prescriber with two telephone calls. If we are unable to contact the prescriber, then, we follow that up with a traceable letter to the prescriber.

If that is also unsuccessful, we then focus on the patient where we do the two phone call attempts to the patient, and if that is unsuccessful, we follow that up also with a traceable letter.

The reason we do this is to ensure that there are no undetected pregnancies out there.

[Slide.]

The patient path for males and female patients of non-child-bearing potential is now on the screen. It again starts with identifying the patient to receive isotretinoin. The prescriber determines that this is not a child-bearing

potential patient, in which case there is no screening pregnancy test required.

Similarly, the prescriber educates, counsels, and registers this patient in iPLEDGE, and upon completion of the registration, this patient can then be confirmed on that visit in the system. There is no 30-day wait for males or female patients of non-child-bearing potential.

At that point, the patient can then take the prescription to the pharmacy and have it authorized, and the authorization process for these patients is identical. The patient then receives a 30-day supply of isotretinoin, and again must wait 23 days, at least 23 days to receive the next prescription.

[Slide.]

This is a picture of all the educational materials that have been created for iPLEDGE for each of the users.

[Slide.]

Materials created specifically for prescribers include:

A Guide to Best Practices, which is an enhanced manual over the previous risk management program's guide.

A Contraception Counseling Guide, which is provided to assist the prescriber in counseling this patient on contraception if the prescriber chooses to provide the counseling him or herself.

We also provide checklists to the prescriber to be used at each office visit for each patient. Both of those are new to the program.

There is a guide for recognizing psychiatric disorders in adolescents and young adults, and that is also an enhanced guide over the previous risk management programs.

There is a DVD that contains two videos to be shown to the patient. These are enhanced over the previous risk management programs.

There is also a reference flowchart to be used by the prescriber in day-to-day practices.

[Slide.]

All of the pharmacy materials are new for the iPLEDGE program, and they include the

Pharmacist Guide, a supply of prescription bag stickers to be placed onto the bag prior to dispensing, as well as a reference flowchart for the pharmacist.

[Slide.]

Patient materials are tailored as to the type of patient they are, whether they are a female patient of child-bearing potential, or the other category are the males and the females not of child-bearing potential.

The FCBP materials include:

A Program Guide to isotretinoin.

A Birth Control Workbook, which is provided to the patient to assist her and to educate her on contraception to help her make her contraception choices. This is a new book for iPLEDGE.

The Contraception Referral Form and Contraception Counseling Guide. This is given to the patient to take to another healthcare provider if she is referred somewhere else to receive her contraception counseling. This guide then assists

that healthcare provider in helping her make the correct choice for contraception.

The patient kits also include a patient ID, which contains the unique patient identifier for this patient to be used in iPLEDGE, as well as the two consent forms required for each female patient of child-bearing potential, and a reference flowchart for her.

[Slide.]

The males and females of non-child-bearing potential have also an enhanced program guide, the single consent form that they are required to fill out, their patient ID, and their flowchart.

[Slide.]

Specific program requirements.

[Slide.]

Registration and activation of the prescriber starts with the prescriber obtaining the registration form. This can be done either through the Internet or on the phone. They then complete the registration form, sign it, and they can either fax it back or mail it back to iPLEDGE.

Upon receipt of the registration form, we complete the registration in iPLEDGE and then provide back to the prescriber their user name, their password, and their educational kit.

Once the prescriber receives this information, they are able to review the educational material and then log onto the system and activate, which is where they attest to understanding and following the requirements of iPLEDGE.

The activation itself can be performed either on the Internet or on the phone, but we do recommend you use the Internet. It is much faster and much easier to complete.

Once the activation is complete, the prescriber is then mailed the initial set of patient educational kits, and the prescriber can begin prescribing isotretinoin to patients.

[Slide.]

Additional prescriber requirements. As you just saw, we have to register and activate initially. The activation expires annually, so we

require reactivation annually. They must agree to counsel all patients on isotretinoin. They can only prescribe a maximum 30-day supply to any patient in any one month.

[Slide.]

They must agree to register all patients in iPLEDGE, and signify, as part of the confirmation and registration, that they have obtained the signed informed consents from the patient, and that they have provided the appropriate education and counseling to this patient.

[Slide.]

Specific requirements for female patients of child-bearing potential.

There is the additional informed consent about birth defects. They must receive the appropriate contraception counseling.

The prescriber must signify that the patient has selected and committed to using two forms of contraception 30 days prior to therapy, while on therapy, and 30 days after therapy.

The female patient of child-bearing potential must have the negative pregnancy screening test before registration and obtain monthly laboratory pregnancy tests.

[Slide.]

The process for pharmacy registration is similar to the prescribers. They obtain the registration form through the Internet or through the phone. They complete their registration form, and this is completed by a responsible site pharmacist. They are responsible to perform these actions on behalf of the pharmacy.

They return their signed form back through a fax or the mail to iPLEDGE. Upon completion of registration from iPLEDGE, we then send the RSP their educational materials including their user name and password.

They then train the other pharmacists that will be dispensing isotretinoin on this process, and after that, they complete by activating in the system again attesting that they understand the requirements and that they are able to follow these

requirements.

Once they have activated the pharmacy in the system, they are then able to authorize and begin dispensing through iPLEDGE.

[Slide.]

Specific pharmacy requirements. As I mentioned before, they have to pick a responsible site pharmacist to act on behalf of the pharmacy. The RSP is required to register and activate initially, as well as activate annually as their activation also expires annually.

They must agree to authorize all prescriptions through iPLEDGE, to only dispense a 30-day supply, and to provide the Medication Guide that is provided with the packaging.

[Slide.]

As I mentioned, the responsible site pharmacist is responsible to register the pharmacy, to activate and attest to following the requirements, and training all other pharmacists, and they are also responsible for maintaining a training log to prove that this training has been

performed.

[Slide.]

Wholesaler Registration. We needed to register wholesalers in the iPLEDGE program because we need to track the product flow data, and since the wholesalers are a large part of that data, we must register them in iPLEDGE to be able to complete that product flow data.

The wholesalers can request to receive an agreement. They can receive that by mail. Once they complete that, they sign it, send it back to iPLEDGE, and their registration is complete. They can fax or mail that in, and there is no activation for the wholesaler group.

[Slide.]

In order to receive and distribute isotretinoin, the wholesalers must register annually. They don't activate, but they do have to register annually, and they have to agree to the other wholesaler requirements.

[Slide.]

They can only distribute FDA-approved

isotretinoin. They can only ship to a pharmacy that is licensed in the United States, registered and activated in iPLEDGE. They can also ship to other wholesalers with prior written consent from the manufacturers.

In order to confirm if a pharmacy is eligible to receive isotretinoin, the iPLEDGE system sends daily updates to the wholesalers of a list of registered and activated pharmacies.

[Slide.]

The wholesalers must agree to comply with inspections of their records for verification of compliance. They must agree to return to the manufacturers any isotretinoin on hand if they choose not to register initially, re-register, or if the registration is revoked.

They must agree to provide the product data flow, and it is important to note that this data is only provided to the manufacturers and the FDA. It is not shared with anyone else.

[Slide.]

Christine Mundkur had a slide that touched

on stakeholder feedback. I will now provide some specific examples and our responses.

The AAD initially raised the concern of additional prescriber burden and delegation of those duties, and iPLEDGE responded by creating the Office Staff Designee Function. This is where an office staff can register in iPLEDGE and then can perform all patient functions in the system on behalf of the prescriber.

There have been some questions raised around the 7-day window definition as to when it starts, the duration, and what happens if you miss it. We are under evaluation of the 7-day window and possibilities of changing that.

There have been some operational hurdles that have been raised by the AAD, and we have heard their concerns, and we are committing to working with the AAD to resolve these issues.

A very simple example of this is recently, there was some concern raised on ordering materials on the system. The link for prescribers to order materials is very difficult to find, and we have

recently added a link on the prescriber's home page, which is a button very easy to find.

The National Association of Chain Drug Stores initially raised concern over the lack of centralized functionality in iPLEDGE for chain pharmacies. iPLEDGE was designed to register and activate a single pharmacy at a time, not as a corporation.

We responded to this by providing some alternate methods of registration, as well as activation. We now have ability to register and to activate multiple stores at one time.

Additionally, NACD has raised concern about electronic prescription authorization, which through iPLEDGE is not conducive to their normal pharmacy processes, and we have taken that under evaluation.

The Health Care Distribution Management Association raised a concern about the updates to them, the daily updates of the list of eligible pharmacies, and we have responded by providing them a 24-hour grace period upon receiving this list in

order to get that into their systems for their order processing.

[Slide.]

Status update of iPLEDGE.

[Slide.]

On December 30th, that was the mandatory date for wholesalers and pharmacies if they wanted to continue distributing and dispensing isotretinoin, they had to be registered in iPLEDGE. Patient registration began on December 30th.

On December 31st, there was an initial request for product return that went out to any unregistered wholesaler or any pharmacy that is registered, but does not intend to activate in iPLEDGE. They were required to return the product on hand at that time.

We followed that up on January 31st with an additional request for product return to any pharmacy that was registered and still had not activated in iPLEDGE. They were required at that time to return all product on hand.

The last date to fill a prescription in

one of the previous risk management programs is February 28th, with March 1st being the mandatory date for all stakeholders in iPLEDGE.

[Slide.]

The registration and activation numbers for each of the stakeholders. Currently, we have over 48,000 retail pharmacies registered in iPLEDGE, with over 42,000 of these activated at the current time.

Prescribers, we have over 20,000 prescribers registered, with over 10,000 activated.

We currently have 199 wholesalers registered in iPLEDGE, and we have over 17,000, almost 18,000 patients registered in iPLEDGE, and we are getting over 1,000 registrations a day for the patients.

I will join my colleagues for the questions and answers.

Questions and Answers

DR. GROSS: A very impressive effort. I wonder if someone could comment on the inefficiencies mentioned by Dr. Thiboutot. Are

those being corrected, how often do they occur, what are the plans?

DR. MILLER: Hi. This is Michelle Miller from Covance. I am the program leader for iPLEDGE.

We have received the comments from the American Academy of Dermatology, and as we receive these comments, we quickly assess those and look at what remediations we can put in place and how quickly.

In the release of the software that went in today, as Jim Shamp had stated, we put in a button around ordering the materials, which was one of the problems that was raised to us that prescribers were having issues.

The second issue that was raised, that Dr. Thiboutot had mentioned that, as well, this morning, was around passwords and the problems with those, as well as call center issues.

What we have done to try to address those as rapidly as we can, we have implemented this week additional agents on the phones. We have doubled the number of agents who can do password resets,

and we are in the process of tripling the number of agents totally who will be available to answer calls in the month of March, and we have already increased for February, as well. My apologies.

So, we believe that we are doing what we can to address these as they come up. It takes a couple weeks to respond to the change and probably another couple weeks for the community to really feel those changes.

DR. GROSS: Henri.

DR. MANASSE: I have a number of questions. First of all, are these medications available in hospitals and outpatient clinic pharmacies, and if so, what kind of efforts have been engaged in to register them and to get the pharmacists involved?

Secondly, we talk about pharmacies and we talk about pharmacists. There is a big difference between the two. That is particularly a critical issue in terms of corporate pharmacy, which is represented by the National Association of Chair Drug Stores versus the pharmacists who are the

front-line practitioners who are interfacing between the product and the patient, represented by their professional societies.

To my knowledge, being a professional society, I have never received any correspondence about how we must educate our members about this particular program.

So, I would like to get a little bit more detail on that.

Thirdly, we have gotten rather intensive suggestions from both Congressman Stupak and the AAD. I think we need to address some of those issues and the status of how you all are responding to those, because those are pretty serious issues.

I would also like some response to the recommendation by AAD whether or not the implementation of iPLEDGE should be deferred to a later time.

DR. MILLER: Michelle Miller again from Covance.

DR. GROSS: You had better not sit down.

DR. MILLER: Okay, or I can just get lots

of exercise.

Let me just try to answer the first two of your questions, which were, if I understand correctly, were about the breadth of which we went out to communicate with the pharmacies, not just the chains.

So, let me point back to one data point, which is there were 72,000 registration packets sent out to pharmacies based on the data we received from NCPDP, which is the National--I am sorry, I can't remember the acronym right now, I don't want to kill it.

So, we sent out 72,000 registration packets. In addition, we sent out, to the same list, we sent out Dear Healthcare Professional letters back in the September time frame. In addition, on the Scientific Advisory Board, not only do we have representation from the chain drug stores, but we have representation from the independents, as well.

DR. MANASSE: You are still missing 6,000 hospitals, though.

DR. MILLER: The 6,000 hospitals would have been part of the 72,000, I believe, that we sent the letters out to originally.

DR. MANASSE: So, you sent it to all licensed pharmacies then.

DR. MILLER: All licensed eligible pharmacies based on the packaging of the product of who was eligible to dispense isotretinoin.

DR. GROSS: Out of curiosity, can you comment on what this is doing to the cost of the drug?

DR. MILLER: I will let one of my colleagues answer that.

DR. ANVEKAR: Ashish Anvekar, Ranbaxy Marketing.

As of now, there is no plan to increase the cost of the drugs due to this program.

DR. GROSS: Thank you.

Any other questions? Robyn.

MS. SHAPIRO: What happens if the pregnancy tests done after the termination of the treatment is positive?

DR. ACKERMANN SHIFF: This is Susan Ackermann, Hoffman-La Roche.

Can you clarify your question?

MS. SHAPIRO: I mean I presume you want the data for the registry, but in terms of how to help or who is going to help or whether there is any help for that woman who is now pregnant, having been within that 30-day window, what, if anything, happens? Do you just say, well, thanks for the information, bye?

DR. ACKERMANN SHIFF: Well, again the relationship between herself and her healthcare practitioner will determine what the outcome will be for that individual woman.

To your point, we are collecting root cause analyses information to try to continually improve the program to ensure that women don't get pregnant in the 30 days post therapy.

MS. SHAPIRO: I mean possibly, and maybe probably, the treater is not going to be the person who will be able to follow up a problem pregnancy, so I am just wondering if you have any other

educational materials or what you do to follow up on that problem, or what you think anybody does or should do.

DR. ACKERMANN SHIFF: Well, physicians will certainly follow the patient through if she chooses to continue with her pregnancy. We do, in Drug Safety, do post-follow up of--

MS. SHAPIRO: The dermatologist will follow her through her pregnancy?

DR. ACKERMANN SHIFF: Hopefully, she will have an Ob-Gyn who will give her appropriate care.

MS. SHAPIRO: That's the point, that's the question.

DR. THIBOUTOT: If, unfortunately, that were to occur, I would immediately call a colleague in Ob-Gyn or another person that could assist with this.

I would hope that on the part of any physician dermatologist, clearly, you are not prepared to deal with pregnancy issues, and we would rely on our colleagues for that.

DR. GROSS: For the record, could someone

review the reason that males and women who are not going to become pregnant are part of the program?

MR. SHAMP: I believe your question is why are males and female patients of non-child-bearing potential part of the program.

The reason for that is, first of all, it was a requirement given to us I believe from the advisory committee, and additionally, we needed to be able to create a baseline of data of the number of patients participating in iPLEDGE, and we could only do that if we registered everyone, as well as accurate data on prescriptions being filled through iPLEDGE.

If we didn't register and authorize each of these patients through iPLEDGE, we would not be able to then verify authorization and have the complete picture of the number of prescriptions authorized through iPLEDGE.

DR. GROSS: Stephanie.

DR. CRAWFORD: Thank you, Mr. Chair.

First, I would just like to reiterate what Dr. Manasse said again. It is the same thing I

said when this issue was brought to our committee before. There is the need to make a clear differentiation when you are referring to pharmacies versus pharmacists, because I think sometimes you are using them synonymously, and there is a difference.

I have three quick questions that I will put out at the same time, so the people who can answer can come up.

The first question is, for females of child-bearing potential, the requirement for two forms of contraception, realizing that some people will have personal reasons for abstinence, what will be done in those cases? Would they not be allowed to receive the drug?

Secondly, who do you consider to be the universe of physicians, being 36,000? There is about 800,000 physicians nationally. So, is it restricted to just certain specialties of physician prescribers?

Lastly, in this very comprehensive program, which I applaud, although, of course,

there are some issues that need to be addressed, there is so much data. I heard it said that the data are confidential to the manufacturers and to the FDA.

My question is, will these data by the manufacturers be used for any purposes other than pregnancy prevention or detection efforts, because in the past, we asked would they be used for marketing or any other use?

DR. ACKERMANN SHIFF: I will answer your first and third questions, and Michelle Miller will answer your second.

With regard to abstinence, as in the current labeling, and the new labeling, abstinence is a form of contraception, and again that relationship needs to happen between the patient and the physician to the choice of contraception.

Now, during that discussion on contraception, she certainly will be offered several other options, and the physician, together with her, will have to make the determination that she is able to be abstinent during the course of

her therapy and for 30 days post-therapy.

In addition, she will still get the educational workbooks and still choose some other methods should she not be able to complete her abstinence.

To your last question, absolutely not. The data is only for risk management purposes. The companies do not see the individual data, only the aggregate data.

DR. MILLER: To answer your question, I think the question is what is the origin of the 36,000, because we certainly know there are more than 36,000 prescribers, physicians in the country, we actually sent out over 350,000 Dear Doctor letters based on a number, you know, dermatologists, known types of prescribers.

The 36,000 was based on a combination of those registered in the previous programs, as well as those prescribers who have been known to prescribe at least one script of isotretinoin over a one-year period.

Nothing is precluding any prescriber from

signing up.

DR. HENNESSY: This is a tricky question, because I don't know what the right answer should be, but is the consent form that patients sign also a consent form to be a subject in human subjects research?

I would guess that we would want to evaluate the effectiveness of the risk management program, and such an evaluation would want to be published and therefore human subjects research.

So, then, we are left with a dilemma of do we require participation in human subjects research in order to get treatment, which you are not supposed to do, or the other horn of the dilemma is how do you do human subjects research in a context where you might not have the entire universe of people.

DR. GROSS: Sandy.

DR. KWEDER: I will take that, do the best I can.

This is a little bit of a look from afar. One of the reasons that we no longer have the

survey, the voluntary survey of patients, is for that reason exactly.

OHRP had major concerns about that survey and asking patients to participate even if it was voluntary. There were some rewards given for participation, and they were felt to be inappropriate.

The system that is in place now, that queries patients, is really designed to assess patients' understanding of the risks of the drug and their ability to continue to use it based on that understanding.

The materials have been looked at, and we have discussed those kinds of issues extensively with OHRP to ensure that this is only information collected, is information necessary to ensure the safe administration and use of the drug. It is solely for managing the risks of the drug, and not for what would normally otherwise be considered research purposes.

DR. HENNESSY: That makes sense. Are evaluations of this risk management program going

to be conducted and published, and if so, are they human subjects research, and if so, will they need a waiver of informed consent to be able to do that?

DR. KWEDER: Our understanding is that they would not be, because they are solely for how to manage the risk of the drug.

DR. HENNESSY: When you say that they wouldn't be, you mean evaluations would not be published of it, or you mean that informed consent is not required?

DR. KWEDER: The latter.

DR. GROSS: Terry.

DR. DAVIS: The education component is very comprehensive, and it seems to place a huge time burden on the physician and his or her staff, the pharmacist and the pharmacy, and this is just a curiosity. Are there incentives, are there financial incentives that the drug companies are giving to these people for doing this?

I mean how much time, I would also just be very interested in how much time burden we are talking about, and I say that because a lot of

times physicians say they don't do the counseling or don't do it as well or slow down and make sure the patient understands what they are saying, because of limited time.

DR. GROSS: Who wants to comment on that? Go ahead.

DR. THIBOUTOT: In terms of compensation for their time, there is none. You are absolutely right, and that is one of the major concerns that we have. There is a lot of patient education involved, a lot, and it does take time, and I didn't read through the 14 pages of testimonials that we received from physicians.

It used to be one of the physicians commented, and I have noticed this, as well, that the new materials require on average about 45 minutes of counseling, to go through these materials in depth, and that is what we are required to do.

You add to the 45 minutes of patient time, the time that is being taken away from the patients, to be held on the phone line for an hour,

that no one is compensating for this, and this is a concern.

It's a concern of practitioners, because as you might imagine, everyone is in some sort of business unfortunately. I hate to say it, but you are, everyone is, and when you have to put this much time into the key component, which is the education of the patient, we are being taken away from that time due to operational issues.

The operational issues at the moment, related to this program, are not only taking away from the time of the iPLEDGE patients, but it is taking away the time from other patients in the practice.

We have one testimonial that I wasn't able to read where the physician's office and the nurse were on hold for 45 minutes. During the hold time, the physician was able to excise a facial skin cancer from his next patient while waiting on hold for the system.

These are the problems. There is no compensation for this time. It is lost time.

There is no compensation for the patient making multiple visits back and forth to the doctor to try to get a prescription.

There is no compensation for the missed visit where the patient comes back and is seen again by the physician, and is maybe having to have the pregnancy test repeated, that we don't know where these monies are coming from.

There is no charges being held, and who is to be held responsible for the extra office visit and the extra pregnancy test, the patient, the patient's insurance company? Should the physicians write this off?

We don't have the answers to these questions, and our major concern is although we saw many of the rules presented today from Jim from Covance, there are a lot of rules that we are not aware of, operational rules, how to enter data into the system, when can we enter data, is it the date of the visit, is it the date afterward?

If a women comes into my office and had her pregnancy test done yesterday afternoon at 4

o'clock, and it's today at 9 o'clock, I am not aware until very recently that yesterday's pregnancy test is not applicable. It has to be a new pregnancy test done at the time of the visit or during the 7-day window.

Most of these operational rules are not known by prescribers.

DR. GROSS: I am Dr. Gross. I am a practicing physician. I have ordered thalidomide for a patient and had to go through a similar process. No sympathy from me.

I think we are concerned about patient safety. If it takes extra time to do it safely, it takes extra time. Under some programs, particularly Medicare program, you can charge for time, but if you can't, our role is really to do the best thing for the patient. If it takes a little more time, tough.

Art.

MR. LEVIN: I want to go back to the logistical concerns, and the reason I keep coming back to it is because I don't want risk management

to get a bad name, and if a program goes into effect that has severe operational difficulties, and end up with the unintended consequence of depriving appropriate patients, appropriate medication, that is not good for anybody, because then everybody says, well, you see what happens when you have these complicated risk management programs. They just are a burden, they get in the way, and that's not a good thing.

So, I guess I would like to hear from FDA and Covance, how comfortable they are with this deadline. What I just heard somebody say is we are working on it, it takes a couple of weeks, and then it takes a couple of weeks to sort of get it out.

Well, a couple of weeks and a couple of weeks is beyond March 1st, folks, so if that is the case, and we are recognizing that, should there be some attention paid to the fact that it is unlikely, if these kinds of problems are that widespread, that it is unlikely that they will all get resolved in a satisfactory way.

You can deal with that in two ways. One

is you can change the deadline, say, okay, we recognize you need another 30 days or 60 days to really get this ironed out and make it work, or you can create sort of an ombudsman program that says, Doc, if you are having a real problem, here is a 24/7 emergency number to call, somebody will be on the other end of that phone and actually answer, and help you resolve that specific problem during this break-in period.

You have got to have one or the other, it seems to me, because I really think it would be tragic if this kind of program got a bad rep because it was depriving appropriate patients of appropriate medication.

DR. GROSS: Does anyone want to answer that?

DR. KWEDER: I will take it, Dr. Gross.

DR. GROSS: Go ahead, Sandy.

DR. KWEDER: I think both of those things, that one may not be enough, because prescribers experiences vary, prescribers office practices vary.

I do want to say that this is, as you have heard, you know, it is always fascinating to me when I see this laid out on the slides, that it all seems so orderly and straightforward, but it is actually much more complicated.

This whole program has taken us, and I think the companies, as well, into areas of controlling distribution that we never really have had to deal with before.

One of the things that we haven't talked about here is the complications of completely understanding the interface that the clinicians don't see, which is the assurance, for example, that only participating pharmacies and distributors receive the medication.

We haven't even talked about that. It is extraordinarily difficult and it is a whole other area of potential risk with diversion of product. Nonetheless, we take the concerns raised by the dermatologists and other clinicians very, very seriously.

We have received communication from them,

you know, well before this meeting, and have already begun to talk with Covance and the sponsors about how that can be addressed, and those issues do need to be addressed.

Some of them are technical issues, technical fixes, I have to say, that gives us great relief that the government is not the only one that has trouble in implementing new IT systems, but they are complex.

On the other hand, as you know, we have other parties who are concerned. You have a letter in your packet from Congressman Stupak saying that the date absolutely should not be extended, under no circumstances, and we have to balance that, but I think ultimately, our goal is that patients and physicians have a system that is workable, because what we don't want is we don't want to drive clinicians and patients to sources where they won't have any education or any safety checks in place.

I also wanted to comment on a couple of things that didn't come up. Several of you have mentioned the difference between pharmacies and

pharmacists. I don't want to give that short shrift.

That has been a substantial point of discussion with the sponsors and Covance, and trying to work out something that is manageable, so that for chain drug stores and large pharmacies that have more than one pharmacist and sometimes multiple working under a particular company, that we have a reasonably sound system of education for the pharmacists who work for those pharmacies, and that each one of them is well schooled in the program and its requirements.

Third, I want to mention that some of the other difficulties that we have encountered, it will come probably as no surprise to you, there are things that isotretinoin is used for outside of treatment of acne.

We have heard loudly from the pediatric oncology community where isotretinoin is, while not approved for this indication, is a standard component, standard of care in the treatment of children with neuroblastoma, and these are very

young children who one would certainly never think need pregnancy testing, and it is also dosed differently than the program seems to allow for.

So, that is another thing that we are working with Covance and the sponsors on, you know, ensuring that those patients, who may not have 30 days to wait, for example, can have access to the medicine. So, just to give you a flavor.

DR. GROSS: Thank you.

Jackie.

DR. GARDNER: The timing on this deadline in pharmacies is coinciding with similar hanging on the phone about Medicare Part D, and the same things. I heard this yesterday, the day before, so I appreciate Congressman Stupak, and we periodically come in here and say how come it has taken two years to do this, that, and the other thing, but I would hope that we could be as reasonable as can be about these things, because they are coincident, well, physicians are doing the same thing, too.

DR. GROSS: Any other comments?

[No response.]

DR. GROSS: My goodness, you are silent.

Yes, where is Tom Fleming when we need him.

[Laughter.]

DR. GROSS: So, it looks as though we are at the end of the meeting. My term is over with May 31st. I am not sure we are going to have another meeting. If we don't, I just want to say this has been an eye-opening experience for myself and the other retiring members of this advisory committee.

We understand the pressures that the FDA is under from the public, the government, and industry, and considering all of that, I think you have really done an amazing job, and I want to congratulate all of the committee members for their intelligence, their idealism, and their sense of practicality.

Thank you all very much.

[Applause.]

DR. GROSS: The meeting is adjourned.

[Whereupon, at 12:10 p.m., the meeting was adjourned.]

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