FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DRUG SAFETY AND RISK MANAGEMENT (DSaRM) AND THE DERMATOLOGIC AND OPHTHALMIC DRUGS (DODAC) ADVISORY COMMITTEES

Virtual Meeting

Tuesday, March 28, 2023

10:00 a.m. to 3:44 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Philip Bautista, PharmD, MPH
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

DSaRM MEMBERS (Voting)

Karim Anton Calis, PharmD, MPH, FASHP, FCCP
Director of Clinical Research and Compliance
Office of the Clinical Director
Division of Intramural Research
Eunice Kennedy Shriver National Institute of Child
Health and Human Development
National Institutes of Health (NIH)
Bethesda, Maryland

Sascha Dublin, MD, PhD
Senior Scientific Investigator
Kaiser Permanente Washington Health Research
Institute
Seattle, Washington

John B. Hertig, PharmD, MS, CPPS, FASHP
Associate Professor and Chair
Department of Pharmacy Practice
Butler University College of Pharmacy and Health Sciences
Indianapolis, Indiana

Collin A. Hovinga, PharmD, MS, FCCP
Vice President
Rare and Orphan Diseases Critical Path Institute
Clinical Associate Professor of Pharmacy
University of Texas at Austin, College of Pharmacy
Austin, Texas

Krista F. Huybrechts, MS, PhD

Associate Professor of Medicine and Epidemiology

Harvard Medical School and Harvard T.H. Chan School of Public Health

Division of Pharmacoepidemiology and Pharmacoeconomics

Department of Medicine

Brigham & Women's Hospital

Boston, Massachusetts

Tao Liu, PhD

Associate Professor of Biostatistics

Department of Biostatistics

Center for Statistical Sciences

Brown University School of Public Health

Providence, Rhode Island

Vincent Lo Re III, MD, MSCE

(Chairperson)

Associate Professor of Epidemiology and Medicine

Center for Clinical Epidemiology and Biostatistics

Center for Pharmacoepidemiology Research and

Training, Perelman School of Medicine

University of Pennsylvania

Philadelphia, Pennsylvania

Mara McAdams DeMarco, MS, PhD

Associate Professor

Associate Vice Chair for Research

Department of Surgery

New York University

New York, New York

Suzanne B. Robotti

(Consumer Representative)

President

MedShadow Foundation

Executive Director

DES Action USA

New York, New York

DODAC MEMBERS (Voting)

Ken Katz, MD, MSc, MCSE

Dermatologist

Kaiser Permanente

San Francisco, California

Brian Green, DO, MS, FAAD

Associate Professor, Dermatology

Medical Director, Teledermatology

Penn State Health Milton S. Hershey Medical Center

Department of Dermatology

Hershey, Pennsylvania

Megha Tollefson, MD

Professor, Dermatology and Pediatric and Adolescent Medicine

Consultant, Department of Dermatology

Mayo Clinic and Mayo Clinic College of Medicine

Rochester, Minnesota

Maria A. Woodward MD MSc

Associate Professor, Ophthalmology & Visual Sciences

Section Chief and Fellowship Director Cornea, External Disease, & Refractive Surgery

University of Michigan

Ann Arbor, Michigan

DODAC MEMBER (Non-Voting)

Ercem Atillasoy, MD

(Industry Representative)

Chief Regulatory and Safety Officer

Jazz Pharmaceuticals

Philadelphia, PA

TEMPORARY MEMBERS (Voting)

Abbey Berenson MD, PhD

Professor of Ob/Gyn

Director, Population and Preventive Health

Department of Ob/Gyn

University of Texas Medical Branch

Galveston, Texas

David A. Chambers, DPhil

Deputy Director for Implementation Science

Division of Cancer Control and Population Sciences

National Cancer Institute, NIH

Bethesda, Maryland

Edward W. Cowen, MD, MHSc

Chief, Dermatology Consultation Service

National Institute of Arthritis and

Musculoskeletal and Skin Diseases, NIH

Bethesda, Maryland

Kort Delost, RPh

Community Pharmacist

Bountiful, Utah

Sonia Hernandez-Diaz, MD, DrPH

Professor of Epidemiology

Harvard T.H. Chan School of Public Health

Boston, Massachusetts

Donna Ludwinski, BSChE

(Patient Representative)

Director of Research Advocacy

Solving Kids' Cancer

New York, New York

Sonja A. Rasmussen, MD, MS

Professor

Department of Genetic Medicine

Johns Hopkins University School of Medicine

Baltimore, Maryland

Brian Salvas, PharmD
Executive Director
Pharmacy Operations
CVS Pharmacy
Woonsocket, Rhode Island

Courtney A. Schreiber, MD, MPH
Stuart and Emily B.H. Mudd Professor of Human Behavior and Reproduction
Chief, Division of Family Planning
Department of Obstetrics and Gynecology
Executive Director, FOCUS on Health and Leadership for Women
Perelman School of Medicine
University of Pennsylvania

FDA PARTICIPANTS (Non-Voting)

Claudia Manzo, PharmD
Director, Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Cynthia LaCivita, PharmD

Director, Division of Risk Management (DRM)

OMEPRM, OSE, CDER, FDA

Jacqueline Sheppard, PharmD

Team Leader, DRM

OMEPRM, OSE, CDER, FDA

Leyla Sahin, MD

Deputy Director for Safety

Division of Pediatrics and Maternal Health

Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Office of New Drugs (OND), CDER, FDA

Tatiana Oussova, MD, MPH

Deputy Director for Safety, Division of Dermatology and Dentistry

Office of Immunology and Inflammation

OND, CDER, FDA

SeVan H. Kolejian, PharmD, MBA, BCPPS

Director, Division of Mitigation Assessment and Medication Error Surveillance

OMEPRM, OSE, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. LO RE: Good morning, and welcome. I'd like to first remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Ms. Chanapa Tantibanchachai. Her email is currently displayed.

Good morning. My name is Vin Lo Re. I'll be chairing this meeting. I'll now call day 1 of the March 28-29 Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee to order. Dr. Phil Bautista is the designated federal officer, and he will begin with introductions.

Phil?

Introduction of Committee

DR. BAUTISTA: Good morning. My name is Phil Batista, and I'm the committee DFO. When I call your name, please state your name and affiliation. For AC members, you may also state

your expertise and role at the meeting. We'll first start with the standing members of the DSaRM.

Dr. Calis?

DR. CALIS: Good morning. I'm Karim Calis. I'm director of Clinical Research and Compliance for the National Institute of Child Health and Human Development at NIH, and I'm also chair of the Institutional Review Board in the NIH Office of Intramural Research.

DR. BAUTISTA: Next we have Dr. Dublin.

DR. DUBLIN: Good morning. I'm Dr. Sascha Dublin from Kaiser Permanente Washington. I'm a general internal medicine and a pharmacoepidemiologist, and much of my research has looked at the impact of medications on pregnancy outcomes, including birth defects.

DR. BAUTISTA: Dr. Hertig?

DR. HERTIG: Good morning. John Hertig. I'm a pharmacist by training and an associate professor and chair of Pharmacy Practice at the Butler University College of Pharmacy and Health Sciences, located in Indianapolis.

DR. BAUTISTA: Dr. Hovinga?

DR. HOVINGA: Hello. I'm Collin Hovinga. I'm the vice president for Rare and Orphan Diseases at Critical Path Institute. I've also a faculty appointment at UT Austin College of Pharmacy as an associate professor. My background is clinical pharmacology and epidemiology, and my training is largely in pediatrics with emphasis in neuroscience, and I come as a trialist and pharmacovigilance person. Thank you.

DR. BAUTISTA: Dr. Huybrechts?

DR. HUYBRECHTS: Good morning. I'm Krista Huybrechts. I'm an associate professor of medicine at Harvard Medical School and epidemiologist at Brigham and Women's Hospital. I co-direct a Harvard program on perinatal and pediatric pharmcacoepidemiology, and my research focuses on drug safety during pregnancy.

DR. BAUTISTA: Dr. Liu?

DR. LIU: Hi. This is Tao Liu. I'm an associate professor of biostatistics at Brown University School of Public Health. I'm a

statistician by training and also a health data scientist. My expertise is data-driven decision making and causal inference.

DR. BAUTISTA: Dr. Lo Re?

DR. LO RE: Yes. My name is Vin Lo Re. I'm associate professor of medicine and epidemiology at the University of Pennsylvania, in the Center for Senior Scholars and the Center for Clinical Epidemiology and Biostatistics, and a senior investigator in the Center for Pharmacoepidemiology Research and Training.

DR. BAUTISTA: Dr. McAdams DeMarco?

DR. McADAMS DeMARCO: Hello. I'm Dr. Mara McAdams DeMarco. I'm an epidemiologist, and I'm now at the NYU Grossman School of Medicine, where I'm an associate professor of surgery and population health. I also serve at the department as the vice chair for research. Thank you.

DR. BAUTISTA: Suzanne Robotti?

MS. ROBOTTI: Hi. I'm Suzanne Robotti. I am the founder of MedShadow Foundation and executive director of DES Action USA. I'm a DES

Daughter, and I'm a consumer representative in pharmacovigilance. Thanks.

DR. BAUTISTA: Next we'll be going with the DODAC members, starting with Dr. Katz.

DR. KATZ: Good morning. My name is Ken Katz. I'm a dermatologist practicing at Kaiser Permanente in San Francisco, California. Thank you.

DR. BAUTISTA: Dr. Green?

DR GREEN: Good morning. My name is Brian Green. I am a pediatric dermatologist at Penn State Hershey Medical Center. I'm also the medical director of our teledermatology offering.

DR. BAUTISTA: Dr. Tollefson?

DR. TOLLEFSON: Good morning. I'm Megha Tollefson. I'm a professor of pediatrics and dermatology, and practice as a pediatric dermatologist at the Mayo Clinic in Rochester, Minnesota.

DR. BAUTISTA: Dr. Woodward?

DR. WOODWARD: Good morning. My name is Maria Woodward. I'm an ophthalmologist and

associate professor at the University of Michigan. I study health services research around decision making and run our telemedicine ehealth programs.

DR. BAUTISTA: Dr. Atillasoy?

DR. ATILLASOY: Good morning. I'm Ercem Atillasoy. I am the industry representative. I am a dermatologist by training. I'm the chief regulatory and safety officer at Jazz Pharmaceuticals. I'm also a voluntary clinical faculty member at the University of Pennsylvania, Department of Dermatology, and member of the American Academy of Dermatology. Also, I've prescribed Accutane for many years. Areas of expertise include this drug in particular; dermatology, risk management REMS programs; product labeling; and product development. Thank you.

DR. BAUTISTA: Next we have the temporary voting members. We'll start first with Dr. Berenson.

(No response.)

DR. BAUTISTA: Dr. Berenson, are you able to

unmute yourself?

DR. BERENSON: Yes. Hi. I'm Abby Berenson. I am a pediatric and adolescent gynecologist and a professor of OB/GYN and pediatrics at the University of Texas Medical Branch at Galveston. I am director of the Center for Interdisciplinary Research in Women's Health, and I have conducted a large amount of research on different methods of contraception.

DR. BAUTISTA: Dr. Chambers?

DR. CHAMBERS: Good morning. I'm David Chambers, deputy director for implementation science within the Division of Cancer Control and Population Sciences at the National Cancer Institute, and focus on efforts to advance knowledge as to how we effectively implement evidence-based interventions in clinical and community practice. Thanks.

DR. BAUTISTA: Next, Dr. Cowen?

DR. COWEN: Good morning. I'm Ed Cowen. I'm head of the consult service at the National Institute of Arthritis and Musculoskeletal and Skin

Diseases. I'm a dermatologist, and I also hold faculty appointments at Georgetown University in the Uniformed Services University of the Health Sciences in Bethesda.

DR. BAUTISTA: Dr. Kor Delost?

DR. DELOST: Hi. Kort Delost here. I'm a community pharmacist, associate professor retired from the University of Utah, College of Pharmacy. Good to meet you.

DR. BAUTISTA: Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Good morning. This is Sonia Hernandez-Diaz, and I'm a professor of epidemiology at the Harvard Chan School of Public Health in Boston, where I direct the program in pharmacoepidemiology, and my research focuses on the safety of medications during pregnancy, with a special interest in birth defects.

DR. BAUTISTA: Donna Ludwinski?

MS. LUDWINSKI: Good morning. I'm Donna Ludwinski. I'm a patient representative. I'm the director of research advocacy for Solving Kids' Cancer in New York, and my son was on the drug of

interest that we're going to be talking about for the next two days, for six months for a cancer indication. He had neuroblastoma. Thanks.

DR. BAUTISTA: Dr. Rasmussen?

DR. RASMUSSEN: I'm Dr. Sonja Rasmussen. I'm a pediatrician and clinical geneticist, and I'm professor in the Department of Genetic Medicine at Johns Hopkins. My research is focused on the effects of medications and infections during pregnancy, especially focusing on birth defects.

DR. BAUTISTA: Dr. Salvas?

DR. SALVAS: Good morning, everybody. Brian Salvas. I'm a pharmacist. I currently serve as executive director of retail operations for CVS Pharmacy, and my accountabilities include dispensing compliance and technology enablement, including REMS dispensing.

DR. BAUTISTA: Dr. Schreiber?

DR. SCHREIBER: Good morning, everyone. Courtney Schreiber. I'm a professor of obstetrics and gynecology at the Pereleman School of Medicine, University of Pennsylvania, and chief of the

Division of Family Planning, and I am a clinical and public health scientist in reproductive health.

DR. BAUTISTA: Next, we have the FDA participants, starting with Dr. Manzo.

DR. MANZO: Good morning. I am Claudia Manzo. I'm the director of the Office of Medication Errors and Prevention in the Office of Surveillance and Epidemiology in CDER.

DR. BAUTISTA: Dr. LaCivita?

DR. LaCIVITA: Good morning. I'm Cynthia LaCivita. I'm the director of the Division of Risk Management in the Office of Surveillance and Epidemiology in CDER, at FDA.

DR. BAUTISTA: Dr. Sheppard?

DR. SHEPPARD: Good morning. I am Jacqueline Sheppard. I am the team leader in the Division of Risk Management at the FDA. Thank you.

DR. BAUTISTA: Dr. Sahin?

DR. SAHIN: Good morning. I'm Leyla Sahin, and I'm a deputy director for safety in the Division of Pediatrics and Maternal Health.

DR. BAUTISTA: Dr. Oussova?

(No response.)

DR. BAUTISTA: Dr. Oussova, are you able to unmute yourself and introduce yourself for the record?

(No response.)

DR. BAUTISTA: We'll come back to Dr. Oussova when she's back in the meeting.

Next we have Dr. Kolejian.

DR. KOLEJIAN: Good morning. My name is SeVan Kolejian, and I'm the director of the Division of Medication Assessments and Medication Errors Surveillance at the Office of Surveillance and Epidemiology, at CDER, FDA. Thank you.

DR. BAUTISTA: We'll go back to Dr. Oussova.

Dr. Oussova, if you're present, are you able to unmute yourself and introduce yourself for the record?

(No response.)

DR. BAUTISTA: Okay. We'll go ahead and move along with the meeting. With that, I'll hand it back to Dr. Lo Re.

DR. LO RE: Thank you, Phil.

For topics such as those being discussed today at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Therefore, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members please take care that their conversations about this topic take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you.

Dr. Phil Bautista will read the Conflict of Interest Statement for the meeting.

Phil?

Conflict of Interest Statement

DR. BAUTISTA: Thank you.

The FDA is convening today's joint meeting of the Drug Safety and Risk Management AC and the Dermatologic and Ophthalmic Drugs AC under authority of FACA of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of the

committees are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to SGEs and regular federal employees who have potential financial conflicts when it is determined that the agency's need for an SGE's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of the committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses, minor children and, for purposes of 18 U.S.C., their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents, royalties, and primary

employment.

Today's agenda involves discussion of proposed changes to the iPLEDGE Risk Evaluation and Mitigation Strategy requirements to minimize burden on patients, pharmacies, and prescribers, while maintaining the safe use of isotretinoin oral capsules for patients.

This is a particular matters meeting during which specific matters related to the iPLEDGE REMS of isotretinoin will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have made concerning the iPLEDGE REMS program.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Ercem Atillasoy is participating in this meeting as a non-voting industry representative,

acting on behalf of regulated industry. Dr. Atillasoy's role at this meeting is to represent industry in general and not any particular company. Dr. Atillasoy is employed by Jazz Pharmaceuticals.

We'd like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have had with affected entities. Thank you very much.

DR. LO RE: Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including IPMG's non-employee presenters, to advise the committee of any financial relationships that they may have with the IPMG, such as consulting fees, travel expenses, honoraria, and interests in the IPMG, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, 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 presentation, it will not preclude you from speaking.

We will now proceed with FDA introductory remarks from Dr. Cynthia LaCivita.

Dr. LaCivita?

FDA Opening Remarks - Cynthia LaCivita

DR. LaCIVITA: Thank you.

Good morning, and welcome. I'm Cynthia LaCivita, and I'm the director of the Division of

Risk Management in the Office of Surveillance and Epidemiology in CDER, at FDA. Today and tomorrow, we'll be taking a close look at the risk evaluation and mitigation strategy, or REMS, for isotretinoin, also known as iPLEDGE REMS. Isotretinoin is approved for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older. It carries the risk of embryo-fetal toxicity. The focus of the meeting will be discussing the requirements in the iPLEDGE REMS, which are designed to mitigate the risk of embryo-fetal toxicity and prevent fetal exposure to isotretinoin.

iPLEDGE is the largest REMS program that links prescribing and the safe-use conditions to the dispensing of the drug. Based on the FDA's drug-use data analysis, the total estimated number of isotretinoin prescriptions dispensed has increased from an estimated 1 million in 2013 to 2 million prescriptions dispensed in 2022.

The objectives of this meeting is not to discuss whether the iPLEDGE REMS continues to be

necessary or if the REMS is meeting its goals. As noted in the FDA briefing document, the agency has determined that the REMS is necessary to assure the benefits outweigh the risks of isotretinoin and the iPLEDGE REMS is functioning as intended, and it has been meeting goals.

This meeting will focus on opportunities to minimize burdens while maintaining a comparable level of safe use. We acknowledge that a REMS that requires special actions by stakeholders inherently impose some burden on the healthcare system. We typically think of burden caused by the REMS as additional efforts or resources needed to complete REMS requirements, such as completing training, documenting that a laboratory test has been completed, or other actions that have been performed, particularly as these actions require the prescriber or pharmacist to step outside their normal workflow.

We do not consider activities that are typically part of clinical care, such as ordering or reviewing test results, as burden associated

with the REMS. We understand that REMS requirements can create unintended barriers to patients' access to the drug, and when possible, we strive to strike a balance between the requirements that ensure safe use and burden to stakeholders and patients. We will not be discussing other serious risks associated with isotretinoin at this meeting, as we don't have those subject matter experts present.

I also wanted to mention that on Friday, March 24th, the FDA approved a REMS modification for the iPLEDGE program that includes technical updates to the system that may aid in improving usability of the REMS platform and the implementation of the REMS for stakeholders. These changes include troubleshooting tips on how to obtain forgotten usernames; the ability to easily print informed consents; the reintroduction of a patient calendar for patients who can become pregnant; Spanish translations of several patient material; and also the ability for designees to start and save patient enrollments, as well as the

access to pending patient enrollments on behalf of prescribers.

Today and tomorrow, we're seeking the advice from the advisory committees on possible additional changes to the iPLEDGE REMS requirement to minimize burden on patients, pharmacies, and prescribers, while maintaining the safe use of isotretinoin oral capsules for patients. I'd like to thank the members of the committees for their time today and tomorrow. We understand that your time is valuable and appreciate your participation in this joint advisory committee meeting.

Dr. Roselyn Epps from the FDA is the first presenter, so, Dr. Epps, I will turn it over to you.

DR. LO RE: Great. We'll now proceed with the presentation from Dr. Roselyn Epps.

FDA Presentation - Roselyn Epps

DR. EPPS: Thank you.

Good morning. I'm Roselyn E. Epps, MD, clinical reviewer in the Division of Dermatology and Dentistry, Office of Immunology and

Inflammation, in the Office of New Drugs, Center for Drug Evaluation and Research. I am presenting the background for the drug isotretinoin, which includes an overview of risk management, the regulatory history, and modifications to the programs.

Isotretinoin is also known as 13-cis retinoic acid. It is a first-generation retinoid which is chemically related to vitamin A. Accutane, the registered brand name, was the innovator drug approved in May 1982. The indication for isotretinoin is for severe, recalcitrant nodular acne in patients 12 years and older. For treatment, the drug is dosed by patient weight. For the treatment duration, it's usually 16 to 20 weeks, typically. This is an example of a patient with severe acne cysts and nodules of the cheeks, lower forehead, and nose areas, pictured before isotretinoin treatment. After treatment with isotretinoin, the nodules and cysts have resolved with minimal scarring.

In 2009, Roche withdrew Accutane from the

market, with Federal Register determination that the product was not discontinued or withdrawn for reasons of safety or effectiveness. Currently, there are multiple isotretinoin products available. Absorica and Absorica LD are marketed under new drug applications or NDAs. Generic isotretinoin drugs have been available since 2002 and are marketed under abbreviated new drug applications, or ANDAs, including Amnesteem, Claravis, Myorisan, Zenatane, and 5 isotretinoin products.

Isotretinoin remains the only FDA-approved drug product available for the nodular acne indication. Isotretinoin is highly efficacious, and many patients require only one course of therapy. Isotretinoin is a known teratogen, which causes isotretinoin embryopathy, which we will discuss now.

In 1982, isotretinoin was assigned Pregnancy Category X, meaning that studies in pregnant women have demonstrated a risk to the fetus and/or human or animal studies have shown fetal abnormalities. There is no benefit of isotretinoin use in

pregnancy. The first report of an infant exposed to isotretinoin with malformation was reported in 1983. The malformations seen can be internal and external. Head and face malformations include macrocephaly or microcephaly; small chin; low set, small, deformed, or absent ears; small eyes; and a cleft palate. Internally, the malformations typically involve the brain, including hydrocephalus; the heart, including conotruncal and aortic arch abnormalities; and malformation or absence of the thymus gland.

Due to risks to the fetus and the pregnancy, a boxed warning was added to Accutane labeling in 1984. Labeling recommended use of a contraceptive method at least one month prior to beginning treatment and conducting pregnancy testing prior to beginning therapy. Also, labeling recommended that a patient who became pregnant must discontinue treatment immediately.

Additional reports of embryo-fetal toxicity were published. In 1984, the Centers for Disease Control, or CDC, identified isotretinoin as a cause

of spontaneous abortion and a specific pattern of defects involving the brain, head and face, and heart. An article by Stern in 1984 stated that of pregnancies reported to the American Academy of Dermatology Adverse Drug Reaction Reporting System and the FDA, 83 percent of the pregnancies resulted in spontaneous abortion or birth anomalies.

In 1985, an article by Lammer, et al., in the New England Journal of Medicine reported outcomes of 154 isotretinoin exposed pregnancies collected from the manufacturer, Hoffman La Roche, the FDA, and the CDC, between September of 1982 and July of 1984. Isotretinoin exposure ranged from 7 to 124 days.

Overall, 13 percent of the infants had major malformations; 8 percent of the pregnancies ended in spontaneous abortion. Elective first trimester abortions occurred in 62 percent of exposed pregnancies, and the outcome was otherwise unknown. For a subset of 36 patients followed prospectively, there were malformations in 14 percent of infants at 22 first-trimester spontaneous abortions. The

majority of infants did not show major malformations.

The authors concluded that the congenital malformations signal isotretinoin or retinoic acid embryopathy, involving the cranium and face, brain, heart, and thymus. There was a high relative risk of 25.6 for selected major malformations for births exposed to isotretinoin when the comparator group was infants born live and stillborn in metropolitan Atlanta in 1982. Therefore, soon after approval, pregnancy exposure to isotretinoin was identified as a cause of severe, life-threatening, human birth defects, which may occur after taking any amount, even for short periods of time. In 1985, there was no consistent means to determine prenatally and accurately whether or not a fetus had been affected.

The agency has organized 11 advisory committee meetings regarding isotretinoin, each of which included expert committee member discussion, open public comment, and recommendations. This presentation will highlight the pertinent advisory

committee meetings and modifications.

Beginning in 1988, the FDA convened an advisory committee meeting to discuss ways to mitigate pregnancy risk. Afterwards, the manufacturer instituted the Accutane Pregnancy Prevention Program or APPP. The APPP was a new education-based program with reminder tools for stakeholders, and included messaging; promoting negative pregnancy testing before beginning therapy; monthly pregnancy testing; and limiting prescriptions to a 30-day supply. Stakeholders were not required to comply or participate.

In 2000, the Dermatology and Ophthalmology Advisory Committee, or DODAC, recommended linking a negative pregnancy test to dispensing isotretinoin, mandatory registration of patients and prescribers, and initiating voluntary pregnancy registry. In October 2001, the system to manage Accutane-related teratogenicity, SMART program, was initiated. This was a sticker-based program with individualized stickers applied to each prescription. The sticker intended to verify: conducting two negative

pregnancy tests before beginning therapy; use of two forms of contraception to prevent pregnancy; and a signed consent form. A medication guide was developed, and a prescription compliance survey was implemented to assess the program.

When generic isotretinoin drugs were approved and marketed in 2002 and 2003, each manufacturer started their own safety programs. Coordination between programs was difficult, and there was no centralization. In 2004, the Drug Safety and Risk Management, or DSaRM, Committee and DODAC held a joint advisory committee meeting. The committee recommended registering pharmacies, as well as patients and prescribers. Isotretinoin dispensing should be linked more closely to the negative pregnancy tests. The pregnancy registry should also include root cause analysis, and all manufacturers should participate in a single-risk minimization action plan known as a RiskMAP.

In 2005, the iPLEDGE program was developed as a single consolidated risk management program. All isotretinoin product manufacturers participate

with and operate the program. The risk evaluation and mitigation strategy goals of the iPLEDGE program are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions. This was the first performance-linked access system for isotretinoin so that only registered and qualified patients receive the drug.

The iPLEDGE program risk evaluation and mitigation strategy, or REMS, included certain elements to assure safe use. The elements included certification of prescribers and pharmacies. Enrolled patients were qualified, requiring documentation of monthly counseling for all patients. For those identified as females of childbearing potential, the terminology at the time, monthly documentation was required for pregnancy testing, patient comprehension questions, and the chosen contraceptive methods. Moreover, the voluntary pregnancy registry expanded to include root cause analysis.

For initially qualified patients who can become pregnant, certain steps were required. The prescriber registered the patient in the iPLEDGE program after counseling, identifying two forms of contraception and obtaining a negative screening pregnancy test. Thirty days later, a confirmatory negative pregnancy test and counseling were documented in the system, then the patient was allowed 7 days to pick up their prescription. If the prescription was not filled, the patient was required to wait 23 days and repeat and confirm the negative pregnancy test before filling the first prescription in a registered pharmacy.

For patients who cannot become pregnant, formerly categorized as female of non-childbearing potential, or male, the prescriber registered the patient in iPLEDGE after counseling the patient regarding teratogenic risk and safety. Then the qualified patient filled the isotretinoin prescription in a registered pharmacy. All patients needed to pick up the prescription within 7 days. If not, the patient entered into a 23-day

lockout period.

The iPLEDGE program was initially approved in 2005, and the transition was complete by March 2006. The transition was difficult. Stakeholder registration and activation were slow, resulting in call center overload. Many prescriptions were denied, resulting in treatment delays for patients. As a result, also in 2006, the program removed the 23-day lockout for patients who cannot become pregnant. No labeling change was required. This modification increased flexibility for this cohort and reduced the treatment interruptions for these patients and the burden for prescribers and pharmacies.

In 2007, a joint DSaRM and DODAC advisory committee meeting discussed enrollment recommendations and pregnancy data. After the 2007 advisory committee meeting, additional modifications occurred. The term "childbearing" was changed so that the platform used females of reproductive potential and females not of reproductive potential.

For patients of reproductive potential, the 23-day lockout, after missing the 7-day window, was eliminated for isotretinoin refills. If the initial 7-day prescription window is missed, the interval to repeat the pregnancy test should be at least 19 days since the confirmatory negative pregnancy test, but it was formerly at least 23 days. Also, the 7-day prescription window was linked to the pregnancy test date rather than the date of the office visit, and for those who cannot become pregnant, the time interval to pick up prescriptions was extended from 7 days to 30 days without a lockout period.

In 2008, the sponsors developed a non-compliance policy for manufacturers, distributors, pharmacies, and prescribers, but not for patients. Examples of non-compliance with program requirements include an unregistered stakeholder prescribing, dispensing, or distributing isotretinoin; not confirming counseling; reporting a negative pregnancy test when no test was conducted; or inaccurately

identifying patient pregnancy risk.

In 2009, the modifications included more definition of pregnancy potential. Urine pregnancy test for hCG could be qualitative or quantitative with a sensitivity of 25 milli-international units per milliliter. The confirmatory pregnancy test should be obtained at menses onset in a CLIA-certified lab. Abstinence as a contraception method within iPLEDGE was clarified, and functionally, the system allowed certain changes without call center interaction.

The purpose of the 2011 advisory committee meeting was to discuss whether the iPLEDGE program continued to assure the safe use of isotretinoin; there was undue burden on patients who require access to isotretinoin therapy; and if there were ways, to the extent possible, to minimize the impact of iPLEDGE on isotretinoin access on healthcare delivery.

In 2012, the DSaRM and DODAC Joint Advisory Committee meeting evaluated the FDA's framework for strategies to mitigate the teratogenic risk of drug

products, in general. The discussion included identifying at-risk populations and the benefits and risks when considering mitigation methods for particular populations and conditions to be treated. Since the last advisory committee meeting, the multidisciplinary team has continued to review the program for clarity, safety, as well as the requirements. Pregnancy and safety data are reviewed, as well as iPLEDGE educational materials. Minor and major modifications have been made to the REMS, and stakeholder input has been received to inform the team.

In 2014, the FDA published the Pregnancy and Lactation Labeling Rule, also known as the PLLR. The key change was the removal of pregnancy categories from labeling, including pregnancy Category X from isotretinoin products. The categories were replaced with narrative summaries of risk. Consequently, when Absorica LD was approved in 2019, the combined Absorica and Absorica LD labeling applied the PLLR requirements. This is the boxed warning, with the warning

regarding embryo-fetal toxicity.

Instead of Pregnancy Category X, the language states that isotretinoin is contraindicated in pregnancy. Any patient who becomes pregnant while taking isotretinoin should stop the drug immediately and consult with an obstetrician/gynecologist experienced in reproductive toxicity for evaluation and counseling.

In 2016, Dr. Kenneth Katz wrote a viewpoint piece in JAMA Dermatology describing difficulties for LGBTQ-plus populations. Prescribers and designees were required to assign pregnancy risks for each patient into the system by gender, as well as the ability to become pregnant. This was considered a safety and risk issue by the Agency. Also, if the pregnancy risk for a patient is misidentified, the iPLEDGE program considers misidentification a compliance issue. Subsequently, the FDA initiated a review of the topic and received stakeholder input up to the Center Director level.

In 2021, after discussion with the sponsors, a change in the terminology of patient pregnancy risk categories was approved, eliminating gender labels. The category female of reproductive potential became patients who can get pregnant. Female of non-reproductive potential and male categories were combined into the category of patients who cannot get pregnant. During this meeting, the terminology "get pregnant" will be used interchangeably with "become pregnant." This change in categories affects patients and prescribers.

After several months of information sessions, correspondence, and platform pop-up messages, in October of 2021, the iPLEDGE program announced to stakeholders that there would be a transition of the iPLEDGE system in December 2021. There would be no change in the safety requirements; however, the important changes were, risk management authorization, or RMA numbers, to fill prescriptions must be obtained through the iPLEDGE program website or interactive voice

response system, and the three patient categories would be consolidated into two pregnancy risk categories: patients who can get pregnant and patients who cannot get pregnant.

In December 2021, the iPLEDGE program transition was difficult logistically. At launch, online access to the iPLEDGE platform was difficult for all stakeholders, resulting in delays. Multiple meetings were held with the sponsors and the stakeholders for input. Within months, platform operations improved significantly so that patients could access the medication, although agency re-evaluation remains ongoing.

In summary, the Agency's multidisciplinary team monitors isotretinoin pregnancy risk mitigation and safety programs. The iPLEDGE program has been in operation for 18 years, with complex interdependent features and requirements and ongoing systematic evaluation and modification. In conclusion, there are benefits to isotretinoin for patients with severe nodular acne who do not respond to other treatments. The risks and

consequences of an exposed pregnancy are serious; therefore additional actions have been implemented, and some inconvenience is expected to ensure safe use and to prevent harm.

Thank you for your attention. The next FDA speaker is Dr. Wenjie Sun.

DR. LO RE: We'll now proceed with presentations from James Shamp and Dr. Sara Ephross from IPMG.

IPMG Presentation - James Shamp

MR. SHAMP: Hello. My name is Jim Shamp. I'm the vice president of Data Intelligence and Program Analytics at UBC. I've over 18 years of experience working on risk management programs, including the iPLEDGE REMS. UBC has been the REMS administrator for iPLEDGE since December 2021. On behalf of the sponsors, I would like to thank the FDA and the committee for the opportunity to present to you today.

The iPLEDGE risk evaluation and mitigation strategy, or REMS, is a safety program to minimize the risk of isotretinoin teratogenicity and to

minimize fetal exposure. The REMS is required by the U.S. Food and Drug Administration to help ensure the benefits of isotretinoin outweigh its risks. We are here today to discuss proposed changes to the iPLEDGE REMS requirements to minimize burden on patients, pharmacies, and prescribers, while maintaining safe use of isotretinoin oral capsules for patients.

In this presentation, I will provide an overview of the iPLEDGE REMS and how it has evolved over time. In addition, I will show you the evidence that supports that iPLEDGE --

DR. BAUTISTA: Hi. This is Phil Bautista. I apologize, Dr. Shamp, for stopping the presentation. I just want to make sure we're showing the correct slides up here.

(Pause.)

DR. BAUTISTA: Thank you so much.

MR. SHAMP: Alright, continuing on, in this presentation, I will provide an overview of the iPLEDGE REMS and how it has evolved over time. In addition, I will show you the evidence that

supports that the iPLEDGE REMS is currently meeting its goals and has consistently met these goals over the course of 17 years of operation. Following my review of iPLEDGE overall, Dr. Sara Ephross will present an overview of the pregnancy registry.

Later today, Dr. Greg Wedin will present the major modifications that have been submitted and now approved by the FDA. These proposed modifications to minimize stakeholder burden have been carefully weighed against the potential to increase the risk of fetal exposure to isotretinoin. In addition, we have a number of experts from the iPLEDGE team here today to help answer your questions. There are seven sponsors who manufacture FDA-approved isotretinoin products. These are the sponsors of the iPLEDGE REMS.

Acne is the most common skin condition in the U.S., with approximately 20 percent being a severe type. Nodular acne is a severe, extremely painful inflammatory acne that requires treatment by a dermatologist. Nodular acne often leads to a decreased quality of life, including increased

emotional distress, depression, and decreased self-esteem.

Isotretinoin is an oral prescription medication used to treat severe recalcitrant nodular acne that is unresponsive to conventional therapy, including systemic antibiotics. Isotretinoin provides complete and prolonged remission of disease activity. Seventy percent of patients achieve a 90 percent reduction in lesion count from baseline by week 20.

These data show that isotretinoin is a highly efficacious drug that provides an important treatment option for patients with severe acne, but while highly efficacious, isotretinoin is a human teratogen that can cause life-threatening birth defects; therefore, it must not be used by patients who are or may become pregnant.

There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin in any amount, even for short periods of time. These increased risks include miscarriage or premature birth, severe congenital

malformations and birth defects, and intellectual and developmental disabilities later in life following isotretinoin exposure during pregnancy.

If pregnancy does occur during treatment, isotretinoin must be discontinued immediately, and the patient should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling. Patients are instructed that they must not become pregnant during treatment or for 1 month after discontinuing isotretinoin treatment.

The severe birth defects associated with fetal isotretinoin exposure include both external and internal abnormalities, as illustrated in the images on the left. External abnormalities include malformation of the skull, small or absent ears, abnormally small eyes, facial dysmorphia, and cleft palate. Internal abnormalities of the central nervous system, cardiovascular system, and thymus gland and parathyroid hormone deficiencies have also been documented. In some cases, these abnormalities have resulted in infant or childhood

death. Today, live births of infants exposed to isotretinoin are extremely rare due to safety initiatives to prevent pregnancy during treatment.

The risk minimization activities for isotretinoin have evolved from nearly 40 years. This slide shows a lot of information, but it is important to understand what is presented here because as these activities evolve, you can see the genesis of many of the requirements in today's iPLEDGE.

These started in February 1984 when a boxed pregnancy warning was added to the label. From 1988 to 1990, the Pregnancy Prevention Program was initiated, and the label was strengthened to contain, among other things, specific information about the birth effects associated with isotretinoin and a recommendation for pregnancy testing, two forms of contraception, and monthly negative pregnancy tests before starting therapy.

Notably, it was not until 1993 that a requirement for pregnancy testing was added to the boxed warning. Because of continued unacceptable

levels of fetal exposure to isotretinoin, risk labeling and mitigation strategies were progressively made stronger, based on FDA and advisory committee feedback.

In the year 2000, the label was updated with a requirement for two negative pregnancy tests prior to the initial prescription, and the DSaRM panel articulated the goals that no patient should begin isotretinoin therapy if pregnant and that no patient should become pregnant while being treated with isotretinoin.

In January 2002, the SMART RiskMAP was initiated, which was the first program linking dispensing of drug to confirm negative pregnancy status. Several similar programs were subsequently implemented by sponsors of generic isotretinoin products. In 2004, the DSaRM committee recommended the initiation of a unified mandatory isotretinoin risk management program with a single centralized pregnancy registry. The iPLEDGE program was approved in 2005, and in March of 2006, the transition to iPLEDGE was completed, and all

previous risk programs were discontinued.

This committee met in 2007 and 2011 to review the program and provide guidance on its further development. In 2008, the prescription window for males and females not capable of becoming pregnant expanded from 7 to 30 days. This is one example of a modification implemented to reduce stakeholder burden for patients, and then in 2010, iPLEDGE was deemed a REMS by the FDA.

There have been a number of major and minor modifications to the iPLEDGE REMS approved by the FDA, including the most recent set in October of 2021, which I will describe in more detail on the next slide.

At the end of 2021, we initiated a system transition because the previous vendor announced that they were no longer offering REMS services. This transition to a new website and contact center did not go as planned, but as a result, we had extensive discussions with stakeholders and FDA as to how to reduce the burden of the REMS while maintaining safety. These discussions led to the

submission of a set of proposed modifications in November of 2022.

As I mentioned on the previous slide, there have been a number of major and minor modifications to the iPLEDGE REMS since 2010. Proposed modifications to the REMS programs must be submitted to the FDA by the iPLEDGE sponsors, and only approved changes may be implemented. This slide lists some key modifications approved and implemented over time. The full list is available in the briefing document or on the FDA website.

Major modifications are defined as changes that have a substantial effect on information about the serious risks or safe use of isotretinoin or the actions that stakeholders must take to comply with the REMS. Modifications to the iPLEDGE REMS are proposed reactively to align with new labeling or FDA guidance and requirements. Modifications have also been proposed proactively in response to stakeholder feedback. Note that minor modifications include editorial updates to REMS materials or the website, which are expected to

have limited effect on the safe use of isotretinoin.

The history of the iPLEDGE REMS modification shows that the program has evolved over the course of time as required and directed by the FDA. You will hear more detail about our most recent proposed modifications to improve the iPLEDGE REMS later today from Greg Wedin, but first I would like to talk about the patient risk categories used in the iPLEDGE REMS.

These patient categories have been referred to by several terms over the life of the iPLEDGE REMS. Prior to the December 2021 transition, the most recent terms used were "females of reproductive potential, females not of reproductive potential, and males." Since the December 2021 transition, the classifications were condensed into two patient categories. The first category is patients who can become pregnant, or PWCBP, which includes cisgender females and transgender males. The second category is patients who cannot become pregnant or PWCNBP, which include cisgender males,

transgender females, cisgender females and transgender males that have undergone a hysterectomy, a bilateral oophorectomy, or are postmenopausal.

The current goals of the iPLEDGE REMS are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin serious risk and safe-use condition. For the iPLEDGE sponsors, this means no patient should start isotretinoin if they are pregnant, and no patient should become pregnant while on isotretinoin.

Elements to assure safe use, or ETASUs, are intended to provide safe access to drugs with known serious risks that would otherwise be unavailable to a patient. The ETASUs for the iPLEDGE REMS include special certification for prescribers and pharmacies who prescribe and dispense isotretinoin, dispensing isotretinoin only to patients who are enrolled in iPLEDGE with evidence of safe-use conditions, such as a negative pregnancy test and confirmation of use of contraception, and a

centralized pregnancy registry for iPLEDGE enrolled patients who become pregnant.

Here is how iPLEDGE implements these ETASUs. The iPLEDGE REMS is a single centralized program for all isotretinoin products. The iPLEDGE system provides a technical infrastructure to support registration and enrollment of stakeholders; a collection of laboratory pregnancy test results before, during, and after therapy; verification of patient qualifications; proactive compliance monitoring and actions; and a centralized pregnancy registry.

The program is a restricted distribution model in which manufacturers may ship isotretinoin only to registered wholesalers who then may ship only to certified pharmacies. Prescribers can only prescribe to enrolled patients, and finally, pharmacies may dispense only to enrolled patients with evidence of safe-use conditions. Each of these activities involve direct interactions with the iPLEDGE REMS to ensure all ETASUs and safe-use conditions are satisfied to ensure traceable links

that are documented in the iPLEDGE system.

Throughout our presentations, you will hear us refer to certain years of the iPLEDGE REMS. The years of iPLEDGE reporting periods do not align with the calendar year. For example, iPLEDGE year 15 ran from March 1, 2020 through February 28, 2021. For the first 15 iPLEDGE years, the sponsor submitted an annual assessment report, where the reporting period ran from March through February of the next calendar year. A bridge assessment report was submitted for year 16, which covered the 10 months from the end of year 15 up to the transition. This was the most recent assessment submitted to the FDA. The next assessment report is due March 1, 2024.

iPLEDGE has a very large patient population. Patient enrollment is now based on one of two patient risk categories, patients who can become pregnant, which is often abbreviated as PWCBP on our slides, and patients who cannot become pregnant, abbreviated as PWCNBP. The categories used in year 16 of females of reproductive

potential, females not of reproductive potential, or males, are noted in parenthesis.

The iPLEDGE requirements are different for each patient risk category. In year 16, there were 297,745 newly enrolled patients, which were about evenly split between the two risk categories. The risk management authorization is the last iPLEDGE system interaction prior to a patient being dispensed isotretinoin.

In year 16, there were more than 1.8 million RMAs obtained. Cumulatively, 4.2 million patients have been enrolled in iPLEDGE and more than 20 million RMAs were obtained. The majority of patients who received at least one RMA in year 16 were between the age of 16 and 29 years of age. The iPLEDGE requirements for the patient who can become pregnant are intended to promote safe use of isotretinoin.

I will now walk you through what interactions with the iPLEDGE REMS system looks like for a patient who can become pregnant. At the initial patient enrollment visit with their

prescriber, they will receive educational materials about isotretinoin and the requirements of the iPLEDGE REMS. A screening pregnancy test performed at this visit should be negative, and they will get contraception counseling by the prescriber or be referred to a contraception counselor.

Patients must be enrolled for at least 30 days before the first prescription. At their next visit, after the patient has used two forms of contraception for one month, or if choosing abstinence, the patient has abstained from having any sexual contact with a partner that can result in pregnancy for one month, a second confirmatory pregnancy test is performed during the first 5 days of their menstrual period, immediately preceding the beginning of isotretinoin therapy. This timing provides the greatest probability that the patient is not pregnant when starting isotretinoin therapy.

The date of the confirmatory pregnancy test starts the 7-day prescription window. Within this time period, the prescriber confirms the patient in the system, documenting the negative pregnancy test

and completion of contraception counseling. The patient is then required to interact with the educational and risk management component of the system to demonstrate their comprehension of the patient requirement.

The pharmacy must interact with the system to obtain an RMA to ensure all ETASUs and safe-use conditions are in place. If not in place, the RMA is denied. When the RMA is obtained, the pharmacist is provided with a do-not-dispense after date. The prescription must be dispensed to the patient by this date. These sets create a 7-day window in which to dispense a 30-day supply of isotretinoin to the patient, minimizing the chances that the patient is pregnant before starting therapy, and safe-use conditions are confirmed in each subsequent month of treatment.

For a patient who cannot become pregnant, at the initial enrollment visit, the patient is educated about isotretinoin and enrolled and consented in the system. The patient is counseled on iPLEDGE REMS requirements, including the

importance of not donating blood or sharing leftover medication, and they are then provided a prescription for no more than a 30 day supply. This, again, is a 30-day prescription window with day 1 being the patient's office visit. Before the patient can access their medication, their prescriber must confirm in the iPLEDGE website that the patient is enrolled and has received counseling.

A registered pharmacy must interact with the system to obtain a risk management authorization. The patient can then receive no more than a 30-day supply of isotretinoin. This process then repeats for each month of treatment. The patient is not required to interact with the system for these monthly interactions.

So how do we know that all of these efforts are effective? There are a number of metrics we use to determine if we are meeting our goals of preventing fetal exposure and informing prescribers, pharmacists, and patients about isotretinoin serious risks and safe-use conditions.

Let's first look at at how we assess if we are preventing fetal exposure to isotretinoin.

The iPLEDGE REMS has had a consistently low pregnancy rate for 16 years, with an average of less than 1.1 pregnancy per 1,000 patients who can become pregnant, who received at least 1 RMA. In fact, this rate has been less than 1 pregnancy per 1,000 patients who can become pregnant in iPLEDGE years 12 through 16, corresponding with March 2017 through December 2021.

As a point of reference, the overall rates of unintended pregnancies in the U.S. was 45 per 1,000 among women and girls 15 to 44 years of age. This is according to research published by Finer and Zolna in 2016 using data from two nationally representative sources from 2011. To our knowledge, this is the most updated and reliable source of information for unintended pregnancies in the U.S. Recall that the vast majority of patients in the iPLEDGE REMS are also between the ages of 15 and 44. In contrast, the iPLEDGE REMS pregnancy rate in iPLEDGE year 6, which corresponds with

2011, was 1.2 pregnancies out of 1,000 patients who can get pregnant.

While isotretinoin is used worldwide, no country has adopted a program equivalent to iPLEDGE. Canada's pregnancy prevention program, for example, is education based and is not a restricted distribution model. This is a similar system to the pregnancy prevention program in the U.S. prior to iPLEDGE. It is less stringent than iPLEDGE in that it only requires informed written consent, 2 pregnancy tests with negative results before starting isotretinoin, and 2 reliable forms of contraception during treatments. However, there is no system in place that monitors compliance with these requirements.

While the overall unintended pregnancy rate was comparable to the U.S. rate, Henry, et al. estimated the rate of pregnancy during isotretinoin treatment for the Canadian pregnancy prevention program to be 16 to 24 pregnancies per 1,000 female patients.

These data support the iPLEDGE REMS with its

restricted distribution model is highly effective in reducing the rate of pregnancy in patients taking isotretinoin. In iPLEDGE years 1 through 16, iPLEDGE detected 516 pregnancies before the patient initiated treatment, which prevented a dispense to the patient when pregnant, and as a result, prevented fetal exposure to isotretinoin.

Now let's turn to the evidence that demonstrates that iPLEDGE meets its second goal, to inform prescribers, pharmacists, and patients about isotretinoin's risks and IPMG safe-use conditions. This goal is also demonstrated by the high percentage of patients responding affirmatively to questions presented to the patient before their first prescription. Specifically, more than 98 percent of all patients who can become pregnant recall being told to avoid pregnancy while on isotretinoin therapy, and over 90 percent recall reading the education materials they were provided.

Patients who can become pregnant demonstrate high comprehension about the use of contraception and the risk of birth defects. These questions

demonstrate the patient's understanding of the iPLEDGE REMS requirements, the birth control the patient has chosen, and the risks associated with isotretinoin. The questions presented to the patient are tailored to the patient's contraception choices. In year 16, more than 95 percent of patients who can become pregnant passed the monthly comprehension on the first try. In addition, you will note that patient comprehension scores were similar between patients who did or did not become pregnant.

iPLEDGE is achieving its goal of informing prescribers about isotretinoin's serious risks and safe-use conditions. This is evidenced by the high rates of comprehension demonstrated by prescribers in the knowledge, attitude, and behavior survey of prescribers. Surveyed prescribers exceeded the comprehension rate goals for all four key risk messages in the most recent knowledge, attitude, and behavior survey, which was performed in 2021 during iPLEDGE year 16.

Pharmacists are also surveyed on their

understanding of four key risk messages relevant to pharmacists. You will note high understanding scores for the first three key risk messages for pharmacist exceeding the goal rates; however, pharmacists have consistently scored low on key risk message 4, which specifically assess knowledge as to whether or not it is permissible for a pharmacy to borrow isotretinoin from another pharmacy. The IPMG is evaluating what improvements are needed in order to meet target goals for pharmacists' understanding key risk message 4.

In conclusion, the iPLEDGE system is meeting its goals of preventing fetal exposure to isotretinoin and informing prescribers, pharmacists, and patients about isotretinoin's serious risks and IPMG safe-use conditions. This is evidenced by very low pregnancy rates, the prevention of pregnant patients from receiving drug, and high comprehension and understanding scores. The iPLEDGE REMS helps to ensure the benefits of isotretinoin outweigh the risks.

I described to you briefly the evolution of

the iPLEDGE REMS and modifications that have been approved by the FDA over time. As you will hear, any proposed modification to reduce stakeholder burden must be carefully weighed against the potential for an increased risk of fetal exposure to isotretinoin. Thank you for your time. Now I'd like to invite Dr. Sara Ephross from Syneos Health to discuss the pregnancy registry.

Dr. Ephross?

IPMG Presentation - Sara Ephross

DR. EPHROSS: Thank you, Mr. Shamp.

Hi. My name is Sara Ephross. I'm senior director of epidemiology at Syneos Health. I have more than 25 years of experience with pregnancy registry. I'll provide a summary of the pregnancy registry and describe the role the registry plays in the REMS. I'll discuss the scope and process for pregnancy registry data collection, including collection of pregnancy and fetal outcomes and reported root cause of pregnancy; for example, failure to use two forms of contraception or unsuccessful at abstinence. And finally, I'll note

that we plan to evaluate opportunity for more streamlined processes and more succinct data collection forms.

Patients who become pregnant while on isotretinoin are eligible for inclusion in the pregnancy registry. The objectives of the registry are to determine the isotretinoin exposure status for each reported pregnancy, document the outcome for each pregnancy, and obtain additional information for each pregnancy to allow for the evaluation of the underlying root cause of pregnancy.

Pregnancies are reported to the pregnancy registry in a variety of ways. About 70 percent of the report comes through the iPLEDGE REMS database. If a positive pregnancy test result and/or the diagnosis of pregnancy is entered into the database, the registry team is alerted and begins follow-up. If a pregnancy is reported by phone, the registry team collects information from the caller. If a patient is discontinued from iPLEDGE due to a pregnancy, the registry team contacts the

prescriber's office to begin follow-up. And finally, all other pregnancy reports from various sources, including published literature, are evaluated for inclusion in the registry.

The current pregnancy registry data collection flow begins with an initial pregnancy report. Exposure status is classified as either exposed, indeterminant, or not exposed. Non-exposed pregnancies are neither reported to the agency nor included in statistical analyses. For pregnancies that are classified as either exposed or indeterminate, initial data is extracted from the iPLEDGE REMS database, including patient demographic, prescriber contact information, and isotretinoin therapy dose and time. Additional information requested from the reporter includes healthcare provider contact information, and for patients only, information for a secondary point of contact and consent to participate in and be contacted by the pregnancy registry team.

Maternal prenatal test results, medication, medical and family history, any noted birth defect,

and pregnancy status are all collected at the initial pregnancy report 30 days later and at each trimester. At the end of the pregnancy, information is collected about the outcome and contact information is confirmed. Finally, for live birth, the registry collects infant birth defects noted, testing results, and medications at three time points up to 12 months of age: 30 days, 6 months, and 12 months.

As part of their initial iPLEDGE consent form, all patients who can become pregnant attest that they understand that in the event of a pregnancy, their information may be shared with the pregnancy registry. When a pregnancy is reported, the registry team provides pregnancy registry patient consent and medical release forms for the patient to authorize the OB/GYN and/or pediatrician to release information to the registry. Overwhelmingly, follow-up occurs with the iPLEDGE prescriber because this voluntary patient consent is not usually given. Pregnancy follow-up occurs at 30 days after the pregnancy report and the

first, second, and third trimesters.

If an infant is born, the registry collects information at birth, 1 month, 6 months, and 1 year of age when unavailable. Importantly, a case is closed once a pregnancy outcome and a reason for pregnancy are obtained; otherwise, the case is considered lost to follow-up.

When collecting data on pregnancy, the registry team attempts to collect the following information: patient demographic, pregnancy test types and results, and information on the course of isotretinoin treatment, which are all extracted from the iPLEDGE REMS.

Data requested from the reporter includes first day of last menstrual period and approximate date of conception; exposure status, exposed, indeterminately exposed, or non-exposed; isotretinoin treatment start and stop dates; root cause or contributing reason for pregnancy; and pregnancy outcome, defined as either elective termination, spontaneous abortion, missed abortion, ectopic pregnancy, stillbirth, live birth, still

continuing -- that is pending pregnancy outcome -- or lost to follow-up.

Pregnancy outcome status, defined broadly as pregnancy outcome known, pregnancy outcome, unknown, or lost to follow-up, has remained stable over the life of the registry. Note that at the end of the year 16 reporting period, December 10, 2021, there were 53 pregnancies that were still continuing; that is pending pregnancy outcome. The outcome of these pregnancies will be updated in the next assessment report. Overall, about one-third of pregnancies reported to the registry have been lost to follow-up.

Over the life of the iPLEDGE pregnancy registry, 2,724 pregnancy outcomes have been reported, with about one-third of these lost to follow-up. At the end of the year 16 reporting period, 54 pregnancies were considered still ongoing, including one from year 15 and 53 from year 16. Once again, the outcome of the still ongoing pregnancies will be updated in the next assessment report. Where pregnancy outcome is

known, the largest number were elected termination, followed by spontaneous abortion. There have been 124 reported live births. These pregnancy outcomes have remained stable through the life of the registry.

The root cause analysis is focused on identifying the reported reasons pregnancies occur. This is important because this information helps to evaluate the effectiveness of the iPLEDGE REMS. The reasons for pregnancy reported by prescribers have been stable over time. The three most common reported reasons are failure to use two forms of birth control or unsuccessful at abstinence, followed by contraceptive failure. For about 25 percent, the prescriber reported the reason for pregnancy as unknown, meaning no additional information was provided. There are fewer than 20 percent of patient-reported reasons for pregnancy, with more than 80 percent missing overall. The three most common reported reasons are did not use two forms of birth control or contraceptive failure, followed by unsuccessful at

abstinence.

Now turning to areas for future pregnancy registry data collection, we recommend continuing to collect pregnancy and fetal exposure information, as well as root cause analysis of reasons for pregnancy. This will continue to inform whether the REMS is meeting its goal and whether changes in the program are needed to prevent further pregnancy. We plan to evaluate opportunities for more streamlined processes and more succinct data collection forms. And finally, we acknowledge the FDA reviews team's conclusion that there is extensive knowledge of the teratogenic effects of isotretinoin. Given this, we support reassessing the value of collecting pregnancy and fetal outcome data.

Thank you, and now I'd like to turn the floor back to the FDA.

DR. LO RE: We'll now proceed with a presentation from Dr. Wenjie Sun of the FDA.

FDA Presentation - Wenjie Sun

DR. SUN: Good morning. Thank you for the

opportunity to present the iPLEDGE REMS requirements to prevent exposure in pregnancy. My name is Wenjie Sun. I am a medical officer and work in the Division of Pediatrics and Maternal Health in the Office of New Drugs at FDA.

Here is an outline of this presentation. This presentation will focus on the REMS requirements for contraception and pregnancy testing in patients who can become pregnant. This presentation will also discuss the rationale for the 19-day lockout. First, I'm going to talk about the contraception requirements in patients who can become pregnant.

How contraception is chosen is based on many factors, including medical conditions, previous adverse reactions, drug-to-drug interaction, correct and consistent use in contraception method, and patient's preference. Medical conditions that can affect prescribing include patient smoking status, chronic and acute medical conditions, and age. One such example is combined hormonal contraceptives are not recommended in patients with

migraines with aura because it increases the risk of stroke. Another example will be combined hormonal contraceptives are not recommended in patients who smoke and is 35 years older because it can increase the risk of thrombo-involved events.

Patients should be allowed to have a choice regarding which form of contraception they use. The form of contraception that is selected should be one that is tolerated and can be used consistently and correctly by the patient. Contraception failure is a major source of unintended pregnancy. There are differences between failure rates observed during the clinical trial conditions and failure rates observed with a typical use condition. Failure rates observed during clinical trial reflect the intrinsic efficacy of a contraception method. Typical use effectiveness rate reflect failure rate during everyday life, including inconsistent or incorrect use.

As mentioned previously, there are differences between contraceptive failure rates

under the clinical trial condition and typical use condition. As you can see in this table, different contraceptive methods have a variable typical use failure rate during the first year of use. Contraceptive methods such as sterilization, intrauterine device, and implantable rod have high inherited efficacy because they are user independent. The report of pregnancy rates found that all studies are low and less variable. The failure rates for these methods are less than 1 percent, as you can see in the first red box depicted here.

For other methods that are more user dependent, such as injections, pills, patches, ring, and birth control pills, inherited efficacy is high, but there is still room for potential imperfect use, such as forgetting to take the pill or failure to return on time for injections, and therefore, they're a wider range of reporter probability of pregnancy, as you can see in this second red box depicted here.

For patients who can become pregnant,

iPLEDGE requires two contraception methods for 30 days or more prior to initiation of treatment, during treatment, and for 30 days after the end of treatment, unless the patient commits to continuous abstinence from having any sexual contact with a partner that could result in pregnancy.

iPLEDGE assess abstinence as a lifestyle choice. The prescriber and the patients are required to document absence within the iPLEDGE platform. The list of primary methods of contraception and secondary methods are included in the table here. The primary methods, which are listed here in no particular order, accepted by iPLEDGE, are those with typical failure rates of less than 10 percent. The secondary methods are backup methods with higher failure rates. The iPLEDGE system also requires matching between contraceptive methods entered into the system from the patients and their healthcare providers.

With internal pregnancy testing, here is a graphic representation of the program and pregnancy testing requirements. Starting at the left part of

the graph, as you can see, iPLEDGE requires patients who can become pregnant to start two forms of contraception 30 days prior to treatment. The patient must complete an initial pregnancy test and then a confirmatory pregnancy test 19 days or more after initial pregnancy test. The confirmatory pregnancy test must be completed at a CLIA-certified lab. During the COVID-19 public health emergency, the CLIA requirement was waived, and patients were allowed to complete their pregnancy test either at home or at a physician's office.

Patients who can become pregnant have a 7-day description window starting the date of the confirmatory pregnancy test to complete all requirements and then obtain prescription. During the first prescription pill, if the patient failed to obtain the prescription within the initial 7 days of the prescription window, then they must wait 19 days or more before completing another confirmatory pregnancy test. The maximum duration of prescription for treatment is 30 days.

Additionally, patients must complete a pregnancy test prior to each refill. The prescription window for the refills are 7 days. If patients fail to obtain the prescription during the prescription window for refill, they may repeat confirmatory pregnancy test without any wait time. Patients who can become pregnant must complete the pregnancy test at the completion of treatment and then 30 days after treatment. Patients must continue two forms of contraceptives for 30 days after treatment.

So why is there a 19-day lockout when the initial 7-day prescription window is missed? The 19-day lockout only applies to the first isotretinoin prescription. Patients who enter into lockout have not started treatment. This is an additional layer of screening to prevent exposure to isotretinoin. The 19-day lockout does not apply to subsequent prescriptions where the patient has already started treatment, and therefore exposure cannot be prevented. The goal there is to minimize exposure.

In the next few slides, I will be discussing the menstrual cycle, ovulation, and the rationale for the 19-day lockout with respect to detecting pregnancy. Here is a picture representing an idealized menstrual cycle. In an adult female, the menstrual cycle lasts anywhere from 21 to 40 days, with average being 28 days. The cycle starts with menses, which the uterine lining is shed. During the first 2 weeks of a menstrual cycle, estrogen is a dominant hormone. The uterine lining proliferates and the dominant follicle develops at one of the ovaries.

After LH surge, which is approximately 14 days prior to the onset of the next menses, ovulation occurs. If no pregnancy occurs, the follicle envelops into corpus luteum, progesterone dominates, and the uterine lining becomes thicker until it sheds again, beginning another cycle.

Hormonal contraceptives work by blocking ovulation via suppression of FSH release and LH surge. Additionally, it also inhibits pregnancy by thickening of the cervical mucus and induced

endometrial atrophy. If a pregnancy occurs after ovulation, the embryo develops and implants approximately a week after fertilization.

This graph shows the median serum hCG result in a study obtained from 109 volunteers after conception. As you can see, no hCG level was detected for a week after conception. This is because the hCG was succeeded by the trophoblasts after implantation, and therefore cannot be detected until 8 to 10 days after fertilization; however, individual variation exists. Because a pregnancy requires time to develop before detection, there will always be a gap of time where a new pregnancy cannot be detected.

This is a graphic illustration of the 19-day lockout for a patient with regular menses who are not on formal contraception. For a patient with regular menses, iPLEDGE requires their confirmatory test be complete within the first 5 days of the menses. A failure to obtain the prescription during the initial 7-day prescription window results in waiting 19 days or more from the date of

the confirmatory test, and that brings a patient to day 20 to 24 nadir of their cycle. Testing around day 20 to 24 of the cycle correlates to the earliest time where a pregnancy conceived during the cycle can be detected.

According to a prospective cohort study of 221 healthy females with regular and irregular menstruation, who were planning on a pregnancy, the subjects were tested daily using urine pregnancy tests with an extremely sensitive immunoradiometric assay with detection limit similar to the serum pregnancy test today. This study found the following. At approximately 7-to-10 days after conception, or day 21 to 24 of the cycle, approximately 40-to-66 percent of pregnancies were detected. At day 14, after conception, which is around the day of the expected menstrual period, 90 percent of pregnancies were detected, and 19 days after conception, 97 percent of pregnancies were detected.

This graph represents patients with unpredictable ovulation, which applies to those

with irregular bleeding, amenorrhea, and those with failure on hormone contraception. Similar to patients with regular menses, in patients with irregular menses and amenorrhea, the REMS also requires confirmatory tests to be complete at a certain time. The confirmatory pregnancy test should be complete after the patient has used two forms of contraception for 1 month, 19 days or more after initial pregnancy test, and immediately preceding to start treatment. However, the REMS do not have requirements for when the confirmation tests should be complete in regards to the menstrual cycle.

Ovulation in this population is random. This graph also applies to patients taking hormonal contraceptives, where the timing of the unanticipated ovulation is unpredictable as a result of contraceptive failure. Waiting 19 days or more allows for detection of 97 percent of pregnancies conceived prior to the wait time, prior to the time of the confirmatory pregnancy test. A detection rate for a pregnancy conceived during the

19 days depends on the time between conception and when the pregnancy test was performed. The longer you wait between conception and pregnancy test, the better the detection.

In summary, the 19-day lockout requirements, although affecting a notable number of patients, continue to provide an opportunity to detect pregnancy and prevent fetal exposure in patients who have not yet begun isotretinoin therapy. The 19-day lockout only applies to the first isotretinoin prescription and start from the date of when the confirmatory pregnancy test was performed.

During the first prescription, a patient who has entered into lockout has not started treatment, and the goal is to prevent exposure to isotretinoin. The 19-day lockout does not apply to the subsequent prescription, where a patient has already started treatment, and therefore exposure cannot be prevented. The goal there is to minimize exposure.

I'd like to take this time to thank you for

your attention, and special thanks to the FDA team's Office of Medication Error Prevention and Risk Management; Office of Pharmacovigilance and Epidemiology; and Division of Dermatology and Dentistry. I'd like to go ahead and turn over the presentation to IPMG.

DR. LO RE: Thank you, Dr. Sun.

We'll now turn to a presentation from Dr. Gregory Wedin from IPMG.

IPMG Presentation - Gregory Wedin

DR. WEDIN: Good morning. My name is Greg Wedin, and I represent Upsher-Smith Laboratories on the iPLEDGE REMS. Upsher-Smith has been a participant in the iPLEDGE REMS since April of 2021. At that time, the iPLEDGE REMS was actively transitioning to a new REMS administrator, website host, and contact center. The iPLEDGE REMS was working under a very tight timeline because the former vendor of the iPLEDGE technology platform and contact center was exiting the REMS support space, effective in December of 2021.

I am here today to describe the

modifications we have proposed to FDA to address feedback we have received during and after the transition, as well as minor updates to the iPLEDGE REMS we have completed since the transition. I will also address components of iPLEDGE that we believe are important and should not change in order to preserve the effectiveness of the program and not introduce unacceptable new safety risks.

The transition to a new website and contact center on December 13, 2021 did not go as planned. There were a number of factors that contributed to the challenges with the transition. Notably, there was the departure of the Legacy system vendor with relatively short notice. Passwords from the Legacy system were encrypted and could not be transferred to the new system, and existing passwords could not be used.

I imagine most everyone on this call has experience with the need to remember passwords for many different websites or apps like your banking accounts or credit cards. It is standard with those sites that if you forget your password, you

have an alternate means by which to recover or reset your password, such as a secret question you are required to answer.

In our case, this was a date of personal significance that the user selected when they joined the site. Maybe it was a birthday or an anniversary. Unfortunately, a large number of users couldn't recall their dates of personal significance. As a result, many could not log on to the website, and this led to a massive influx of calls to the newly established contact center. Many actions were taken to address these challenges, which I will discuss, and we ultimately returned to our pre-transition levels of performance.

During the days and weeks following the transition, the iPLEDGE sponsors were in daily or near daily contact with FDA. We presented data related to the contact center and utilization of the iPLEDGE website. We discussed various strategies to increase prescriber, patient, and pharmacy access to the iPLEDGE website, and to

overcome the influx of calls to the contact center. Our goal was to restore the numbers of stakeholders who were able to log into the iPLEDGE website to pre-transition levels and return to the baseline number of daily calls to the contact center.

Another closely monitored data point was the number of risk management authorizations, or RMAs, being generated by pharmacies, which represented successful utilization of the system by stakeholders, meaning that patients were able to receive their prescriptions. The iPLEDGE sponsors with vendor partners undertook a significant number of actions to fully restore functionality of iPLEDGE without taking down the website and while preserving the safe use of isotretinoin.

There were four key actions initiated. We sent extensive communications out through the medical and pharmacy organizations and through the contact center and iPLEDGE website. We provided troubleshooting tips on the iPLEDGE homepage. We added options to the forgot username and forgot date of personal significance tools to help users

update their accounts and gain access to the website.

The most impactful action we took was to provide emails to prescribers with login links to their accounts, and also provided the ability for prescribers to send these links to their patients and designees. This produced a steady daily increase in logins by these stakeholders. Over the next 4-to-8 weeks, users' access was mostly restored, and the system has been functioning at pre-transition levels for more than a year now.

One key indicator of functionality being restored are the numbers of first-time logins to the new system by various stakeholders. This slide shows the number of prescriber logins over the time since the transition on December 13th of 2021. You will note a rapid rise in prescriber logins during December through mid-January of 2022. This metric is meaningful because prescribers need to log on to the system in order to enroll and confirm patients.

Five days after the transition, we began a targeted email campaign to reach prescribers,

designees, and pharmacists who had not yet logged in, and in early January the get-login link was implemented to facilitate access. There has been a gradual ongoing increase in logins since that time. We see a similar trend here for pharmacies, as shown by the blue line.

Not surprisingly, as the number of physicians and pharmacists who are able to log in increased, the number of calls to the contact center decreased. On the first day, however, there were nearly 1.7 million calls to the contact center. To address the increased call center demand seen during the transition, additional call center agents were added beginning in mid-January, and then more were added in early and mid February.

Over time, this allowed our average hold time, as seen here in the orange line, to drop to pre-transition steady state. Another marker of the return of the program to steady state is the percentage of calls answered in a minute or less, shown here with the blue line. We continue to monitor these metrics weekly, and we report the

results to the FDA monthly.

Finally, this slide shows the total number of approved RMAs post-transition as a percent of the weekly average during the same time period the year before. This demonstrates that within just a few weeks, we achieved successful utilization of the system by prescribers, patients, and pharmacies, meaning that patients were able to receive their prescriptions.

In order to get a real-world view of our progress, we sought the input of community dermatologists regarding their perceptions of iPLEDGE. During the fall of '22, we conducted interviews with 39 community-based dermatologists. Most of these practitioners saw an average of 106 acne patients per month and had between 11-to-50 patients currently on isotretinoin. We were interested in their perceptions about iPLEDGE and modifications that were being considered for proposal to FDA. One of the key questions we asked these prescribers was, "How satisfied were you with the iPLEDGE program?"

Here we see the level of satisfaction, an average of 4.8 out of 7 prior to the transition. Not surprisingly, you will note there was much dissatisfaction during the transition, but after the transition, the prescriber survey felt that we have returned to a pre-transition performance, which aligns with the website and call center data I just shared with you.

During the transition in the days that followed, there was discussion with the FDA and stakeholders in which additional opportunities for improvement were identified. Based on these discussions, we submitted proposed modifications to the program to FDA in November 2022. These modifications balanced the desire for changes that will reduce burden for stakeholders with the need to preserve the foundational aspects of the program, specifically to prevent the little fetal exposure to isotretinoin.

After careful consideration, the iPLEDGE sponsors have identified four potential modifications to the program that we conclude will

reduce stakeholder burden while maintaining the safe use of isotretinoin. I will briefly summarize these now and provide more details in later slides.

First, we propose reducing the number of confirmations to receive drug for patients who cannot become pregnant by extending the confirmation interval to every 120 days rather than monthly as it is today. Second, we have proposed changes to the enrollment process to enable a designee to initiate and complete much of the patient's enrollment. This data can be saved at any time. The prescriber will need to complete the process by reviewing and providing final approval and sign off. You heard this morning from FDA that this modification has been approved.

We will also be restoring the calendar functionality that was available in the prior website application, which will depict the patient's status and provide information on actions needed. This proposed modification has also been approved. Finally, we are proposing some minor changes on the website to help overcome entry

errors, which can delay access to isotretinoin, and you heard this morning, this modification has also been approved.

First, let's discuss the extended confirmation interval for patients who cannot become pregnant. This has been a request from prescribers for quite a long time. It has been suggested that other than the initial confirmation, no other confirmation should be required, or at least no more often than yearly, for patients who cannot become pregnant. The iPLEDGE sponsors have carefully considered this request, and while we cannot support eliminating or extending the confirmation interval to a year, the sponsors are agreeable with a 120-day confirmation interval.

This slide shows the number of patients who cannot become pregnant and how many total months of therapy they received in iPLEDGE in year 16. You will note that the mean duration of treatment is about 5 months and 97 percent of patients complete therapy within 10 months. In the current iPLEDGE system, patients are confirmed by their prescriber

every 30 days, as shown by the red stars on this chart. This means that they have been counseled by the prescriber and have met other safe-use conditions in order to receive a prescription.

As previously mentioned, we are agreeable to extending the confirmation interval for patients who cannot become pregnant to once every 120 days, as shown by the yellow stars. We have recommended a 120-day interval because this would ensure that all patients who cannot become pregnant, treated with isotretinoin beyond the mean duration of therapy, will have documentation of at least one additional confirmation before the end of therapy.

We have proposed this modification to reduce administrative burden on prescribers while maintaining other safe-use requirements. Prescribers are required to counsel their patients with every monthly prescription, and we do not propose any change to this requirement. This 120-day confirmation ensures that for patients who are being treated beyond the usual 4-to-5 month duration of therapy, there is documentation in the

iPLEDGE system that important safety reminders are being reinforced, and that a certified prescriber has deemed that additional therapy is warranted. However, extending the confirmation interval is not risk-free and should be carefully examined by this committee. Now, we can take a look at a 120-day confirmation interval and discuss the benefits and risks of this modification.

Currently, when a pharmacy receives a prescription and obtains an RMA, this indicates that the prescriber has confirmed patient counseling on program requirements in the iPLEDGE REMS website. The patient is only qualified to receive drug during the 30-day confirmation interval. This process and documentation are required prior to each subsequent prescription until the patient completes their course of therapy.

The benefit of the proposed 120-day confirmation interval is a reduction in the administrative burden on prescribers to document confirmation on a monthly basis. This means that

the patient can have a prescription filled when they present a prescription to the pharmacy during the confirmation interval without the need for a prescriber to log into the iPLEDGE system and confirm that counseling on the program requirements have been completed. However, the potential risks of extending the confirmation interval include reduced oversight by a certified iPLEDGE prescriber and an increased risk of drug sharing.

Extending the conformation interval to 120 days puts the patient in the status of qualified to receive drug upon confirmation by the certified prescriber for the duration of the new 120-day confirmation interval. This means that the prescription presented to the pharmacy for each subsequent monthly prescription would not necessarily need to be from the same prescriber who originally confirmed the patient. This is because there is no secondary safety check to ensure that the prescriber is certified with iPLEDGE, so extending the confirmation interval creates a new situation that could potentially be exploited to

circumvent the iPLEDGE REMS requirements.

Additionally, while not a new risk, extending the confirmation interval may increase the risk of drug sharing. For example, a patient may be more likely to share their medication with another person the further along in therapy they get as their condition improves. For these reasons, the iPLEDGE sponsors are agreeable with a 120-day confirmation level but do not support extension beyond 120 days.

Our second proposal, a modification to the patient enrollment process, helps to overcome a burden recognized soon after the transition to the new website in December of 2021. Currently, the iPLEDGE website is designed so that all patient enrollment information is to be entered specifically by the prescriber.

We have proposed allowing designees to initiate and document much of the required enrollment information, including demographic information pregnancy test results and patient categorization. This data can be saved at any time

for completion later. This relieves the prescriber of the burden of entering all the enrollment information when for years, as we have learned, this had often been completed in the Legacy system by designees or other office staff. Importantly, the prescriber will continue to have the responsibility to review the data entered by the designee, attest to its correctness, complete the informed consent or consents with the patient, and provide an electronic signature.

Our third proposed modification addresses the failure to include the calendar functionality for patients who can become pregnant with the transition to the new website. This was quite simply an oversight during the transition, as we focused on the technical aspects of the restricted distribution requirements of this program.

On the screen is a representation of the calendar we will implement after approval by the FDA. This provides a graphical view for patients, prescribers, and their designees of the current month of a patient's course of therapy and program

requirements for the patient. In the example on the screen, the green highlighted calendar days represent the 7-day window for a patient to pick up their prescription. In each of the days on the calendar, if you click the "more" link, it will provide the user additional details of the patient's status, including any pending actions needed by the prescriber or patients.

In this example, the patient may pick up their prescription at the pharmacy, including the permissible time frame for pick up. In addition to these changes, our fourth proposed modification includes website updates for prescribers and designees that we expect will reduce data entry errors and help to reduce delays for patients and receiving drug.

The proposed modifications, we just reviewed were made based on input from stakeholders prior to and following the transition. There are some elements of the program the iPLEDGE sponsors feel must be preserved for the safe use of isotretinoin to continue. These relate to several different

waiting periods, and I will briefly address our rationale for each of these in the upcoming slides.

Two of these waiting periods apply to the initiation of treatment. These are known as the 30-day wait and 19-day wait. Following this, I will then discuss the importance of the abstinence switch wait, and finally, I will address the iPLEDGE sponsors' position on the continued use of at-home pregnancy testing. I will begin with the waiting periods associated with the initial prescription.

These waiting periods are designed to ensure that patients who can become pregnant are not in fact pregnant when they begin treatment. As I mentioned, this applies specifically to their first prescription. For patients who can become pregnant, they must have a negative pregnancy test and be on two forms of contraception or remain abstinent for at least 30 days prior to their first prescription. This 30-day run-in provides time for the patient to receive counseling on contraceptive options and initiate their contraceptive choices,

which may include another appointment, for example, to have an IUD placed, and in some cases the time necessary for certain contraceptives to become fully effective, as with oral contraceptives.

After this waiting period and during the first 5 days of the patient's menstrual cycle, a confirmatory pregnancy test is to be obtained. If the confirmatory pregnancy test is negative, the patient can be confirmed by the prescriber to receive drug. The patient then has up to 7 days during which they must go online to complete comprehension questions and confirm abstinence or their two forms of contraception. At that point, the pharmacy can obtain an authorization to dispense the prescription for isotretinoin.

For the first prescription only, if the patient does not complete these activities and fill their prescription within those 7 days, they are required to wait 19 days before having another confirmatory pregnancy test for the process to continue. So why 19 days? The rationale for the 19-day wait is to ensure the next confirmatory

pregnancy test is completed after the most fertile period of the menstrual cycle has passed. This ensures the patient does not receive and start taking drug during the most fertile period.

The yellow star on day 1 of this graphic represents the first confirmatory pregnancy test taken during the first 5 days of the menstrual cycle, noted in the purple-colored days. The 7-day prescription window is represented by the teal-colored days, and the most fertile window is represented by the pink-colored days. If the patient fails to receive their prescription during the 7-day window, they must wait 19 days from the original pregnancy test for the next confirmatory test, which is represented by the yellow star on day 20. You will note that the 19-day wait requirement gets the patient beyond the most fertile period of the cycle before potentially beginning isotretinoin therapy.

The 19-day wait has been shown to prevent people who are pregnant from receiving isotretinoin. In iPLEDGE years 12 to 17, at least

12 pregnancies have been reported to iPLEDGE for patients who were placed in a 19-day wait. This number is likely underreported, as unexposed pregnancies are not required to be reported to iPLEDGE. It is the iPLEDGE sponsors' position that eliminating the 19-day wait would increase the potential for fetal exposure to isotretinoin; therefore we believe the 19-day wait must remain in place.

Next, we will discuss why we conclude that the abstinence switch wait is an important element to prevent fetal exposure to isotretinoin. The abstinence switch requirement is designed to ensure that patients who are changing their birth control methods do not become pregnant during this vulnerable transition period. If a patient who can become pregnant chooses to switch birth control from abstinence to two forms of contraception, they're treated like a newly starting patient. The patient is required to initiate and use the two forms of contraception for 30 days, and then have a confirmatory pregnancy test completed prior to

receiving their next prescription for isotretinoin.

This requirement mirrors the initial 30-day wait requirement prior to initiating isotretinoin therapy, as I discussed previously. Again, it is important to consider that not all birth control is immediately effective and that pregnancy tests may produce false negative results if obtained shortly after conception; therefore, some wait period is necessary when changing from abstinence to two forms of contraception. Thirty days has been the standard for many years, and the low rates of pregnancy in the iPLEDGE program support continuing this standard.

Finally, I will address why the sponsors conclude that we cannot support continued use of home pregnancy tests. The REMS requirement for a CLIA-certified laboratory pregnancy test was relaxed at the beginning of the COVID-19 pandemic in order to facilitate testing at times when visiting the doctor's office may have been ill-advised or impossible. While we agree that this was an appropriate accommodation during the

time of a public health emergency, there are limitations to at-home testing that make it less reliable than CLIA-certified in-office tests, and therefore could increase the risk of unintended pregnancy.

Specifically, deliberate falsification of results have been occurring at an unacceptable rate. Similar methods of falsification were documented in separate publications by both Smith and Johnson in 2022. Further, there are a variety of factors that may impact the reliability and accuracy of at-home pregnancy test results.

Given these limitations, the iPLEDGE sponsors do not support long-term use of at-home pregnancy tests. However, after reviewing the FDA briefing document and further discussion with stakeholders, we agree that administration of a pregnancy test with a sensitivity limit of at least 25 milli-international units per milliliter administered in a provider's office is an acceptable alternative to using a CLIA-certified laboratory test. We support this proposed

modification.

So to conclude our remarks regarding potential modifications, the iPLEDGE sponsors have carefully considered a variety of suggestions from stakeholders to reduce burden. We have proposed modifications that will reduce burden but will not increase the risk of fetal exposure to isotretinoin. In addition, there are elements of the program that the sponsors feel must be maintained.

Thank you for your time today. We look forward to the continued discussion on the proposed changes to the iPLEDGE REMS to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of isotretinoin for patients. Thank you.

DR. BAUTISTA: Hi. This is Phil Bautista, the DFO. Thank you, Dr. Wedin, for your presentation. Before we begin with clarifying questions for both FDA and IPMG, I wanted to circle back to introductions.

Dr. Oussova, if you're available, can you

introduce yourself for the meeting record?

DR. OUSSOVA: Yes. I can't start my video.

Yes. My name is Tatiana Oussova. I'm the deputy division director for the Division of Dermatology and Dentistry, and participating in this advisory committee. Thank you.

DR. BAUTISTA: Thank you, Dr. Oussova.

I'll hand it back now to Dr. Lo Re.

Clarifying Questions to Presenters

DR. LO RE: Thank you, Phil.

At this time, we will now take clarifying questions. I'd ask that you please use the raise-hand icon at the bottom of the Zoom to indicate that you have a question, and then remember to lower your hand by clicking the raise-hand icon again after you've asked your question. When you're acknowledged, please remember to state your name for the record before you speak, and direct your question to a specific presenter, if you can. If you wish for a specific slide to be put up, please let us know the slide number and the presenter, if possible.

Then finally, it will be helpful to acknowledge the end of your question with a thank you and the end of any follow-up question with, "That's all for my questions," so that way we can move on to the next panel member.

Okay. I see a hand up from Dr. Katz.

DR. KATZ: Thank you. I've got a few questions. This is Ken Katz. The first question is, I think we all want the most effective REMS program that's the least burdensome on everybody involved. One of the things that strikes me is that iPLEDGE seems to be the most burdensome REMS program of all the teratogenic medicines that are out there, and I found that comment 177 in the docket, which is a manuscript from Zaenglein and colleagues, that compares iPLEDGE to other REMS programs, is very useful in explaining why it's so much more burdensome and the ways it's so much more burdensome.

So I think it would be nice to get a sense from the FDA of how effective these other programs are and what are the rates of pregnancy that they

are noting in those programs that are less burdensome. Zaenglein also makes interesting comments about the lack of information about emergency contraception in the iPLEDGE program that could also reduce pregnancy risk, and a question about why a secondary form of birth control is needed for people who are on long-acting reversible contraception.

My second question is regarding the 19-day lockout period and what is the rationale for that if somebody is already on a long-acting reversible contraceptive. Why does that 19-day lockout period not apply to thalidomide or other teratogenic medicines? Why is it unique to isotretinoin?

My third question has to do with the confirmation interval that the isotretinoin group states is permissible or acceptable for them every 120 days. It's my understanding that we're trying to reduce fetal exposure to isotretinoin, and people in that group would be involved with that if they are diverting the medicine or through blood donation. My question is, have there been any

cases of pregnancy exposure linked to diversion or blood donation that we know about so far, and what are the details, if so?

My last question is about the home test issue. Those studies that were cited did show falsification of home tests. There were some mitigation strategies that have been proposed, such as writing names and dates on pregnancy tests, and I'm wondering what the stakeholders think about that as a way to mitigate the risk of falsification. And it seems like the iPLEDGE program is the only REMS programs with a requirement currently, except during COVID, for a CLIA-certified lab testing.

Those are my four questions. Thank you very much.

DR. LO RE: Great. It sounded like two of the questions were directed, Dr. LaCivita, to the agency, and at least to me, it sounded like two of the other questions to IPMG. Can we start with the agency's responses to questions about the lockout if on long-acting contraceptives?

DR. LaCIVITA: Dr. Lo Re, may I actually start with the question that I think was directed about the REMS programs with other teratogenic risks? Would that be acceptable?

DR. LO RE: Absolutely.

DR. LaCIVITA: Okay.

I'm not able to speak today about efficacy or pregnancy rates for other programs. Those sponsors aren't here today, and they aren't participating in the meetings. What I can tell you, though, is there are other programs, and they vary, and it's depending on the indication, the duration of use, and the severity of the embryo fetal toxicity.

There are other programs that actually do have requirements that are very similar to iPLEDGE, depending on those indications, whether it's for an oncology indication, where you may not want to delay therapy for those particular patients. Those requirements differ in that some of those programs require weekly pregnancy tests for the first 4 weeks. If the patient has a regular menstrual

cycle, then they might have pregnancy tests after the first 4 weeks, every 4 weeks. And if they have an irregular cycle, then they would have pregnancy tests every 2 weeks. So they are all a little different from that perspective. I'm hoping that maybe answers some of your questions with regard to that.

I think your second question was regarding the issue with --

DR. KATZ: The long-acting contraception.

DR. LaCIVITA: -- the long-acting contraception. The iPLEDGE REMS is not tailored to contraceptive methods at this point in time. It's done in a way to kind of minimize confusion, so requiring variations within the program, we thought it could be confusing and it could actually lead to poor outcomes.

So I'll stop with those, and hopefully that answers the FDA's comments, and I just want to see if others from the agency have anything to add.

DR. LO RE: Thank you, Dr. LaCivita.

DR. LaCIVITA: Sure.

DR. LO RE: Others from the agency to add?

(No response.)

DR. LO RE: If not, I'm going to turn to the folks at IPMG to respond to Dr. Katz's other two questions. There was a question about reducing the fetal exposure by extending the confirmation 120 days. He asked about how often diverting medication or blood donation has been observed, and if there's any data on that? And then there was a home testing issue question about writing names and dates on iPLEDGE.

MR. SHAMP: It's Jim Shamp from UBC. I think there may have actually been a third question in there as well. I just want to make sure that we're capturing that. I think there was a question about the 19-day wait itself in users using LARC contraception. Is that correct?

DR. LO RE: Yes. You could answer that as well. I know Dr. LaCivita tried to address that as well.

Why don't you start with that one?

MR. SHAMP: The reason we do require the

19-day wait in patients that are using LARCs is that all contraception choices can fail, and it's important that we ensure that that patient is not pregnant prior to starting. As you saw from FDA's presentation this morning, this is the only opportunity that we can prevent exposure, so that is paramount in this case.

To address the question about the 120 days and if we have had any cases of pregnancy in sharing of the drug, we have had several in the early years of iPLEDGE through year 5, and we have most recently had one, but this data has not been provided -- it was in year 17 -- to the FDA at this time.

The third question was the use of home pregnancy tests and could we mitigate any concerns of tests, and I will ask Dr. Greg Wedin to respond to that question.

Dr. Wedin?

DR. WEDIN: Greg Wedin, Upsher-Smith Laboratories. In the reports by Smith and Johnson, there were recommendations that there might be ways

to mitigate that risk, as you've described. I think that before we would want to go down that path, we would need evidence that those sort of mitigations would be effective. Also, it seems to me that those mitigations would create significant burden on patients and prescribers needing to provide pictures with the date written on them, and to receive that information, and to record that information in the patient's medical record.

So it seems that that's a burdensome approach, and as I mentioned earlier, we would need more data to support that that would be effective. Thank you.

DR. LO RE: Thanks, Dr. Wedin.

A question from Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: Hi. This is Sonia Hernandez-Diaz, and I had a question. I think it's more for IPMG, and it is regarding the estimation of the pregnancy rates for comparability between the years and with other publications that have been referenced.

My question is, when you provide the

estimation of the pregnancy rate in a year, how do you consider the months of exposure during that year if they are not 12 months, and the months of follow-up for that particular patient?

MR. SHAMP: Jim Shamp with UBC. The way we calculate the pregnancy rate in iPLEDGE is that we take the number of patients that had at least one RMA, which is the surrogate for having taken the drug and being exposed. We divide that by 1,000 to get the number of patients by 1,000, and then divide the pregnancy rate by that number to calculate the number of pregnant patients per 1,000 patients who receive drug.

DR. HERNANDEZ-DIAZ: Okay. Thank you.

DR. LO RE: Dr. Dublin, do you have your hand up?

DR. DUBLIN: I do. Thank you. I'm Sascha Dublin from Kaiser Permanente. I really appreciate comments other people have raised. I would really highlight the idea about educating people about emergency contraception, but what I want to focus on in a few questions is the monthly counseling

that continues to be required for people not of childbearing potential.

I recognize the effort to minimize burden by requiring confirmation every 120 days, but requiring continued ongoing contact for monthly counseling for people not of childbearing age seems quite burdensome, especially in an era when we have a really big problems with provider access and provider shortage.

So my questions include, what is the evidence we have that given the topics to be covered, that monthly counseling is required rather than, say, every 3 months or every 6 months? What is the the rationale for requiring monthly refreshers of this counseling, and what is the evidence that it's more effective to have a contact with a healthcare provider rather than providing an interactive online educational module that could potentially be automated and spare the healthcare provider the ongoing burden of repeatedly meeting with a patient who we think probably has a very low likelihood of either diverting the drug or doing a

blood donation. Thank you.

MR. SHAMP: Jim Shamp from UBC. The importance of the counseling in the system is that it does provide the documented evidence that this counseling has occurred, and I'll ask Dr. Greg Wedin to further discuss this.

Dr. Wedin?

DR. WEDIN: Greg Wedin at Upsher-Smith Laboratories. The monthly counseling, as has been indicated in our presentations, is intended to reinforce the importance of not sharing drug and to not donate blood. I think it's important that it does not necessarily have to take place during an office visit. Certainly telemedicine has become a very important approach to healthcare, in recent years particularly, so that counseling would not necessarily have to take place in person.

A prescription is required every 30 days, so certainly any interaction that takes place between the prescriber and the patient during that time, at the time of the monthly prescription, that reinforced counseling can easily take place. Thank

you.

MR. SHAMP: To address your questions about other methods of counseling, we certainly appreciate your suggestions of these other methods, and that is something that we'd be happy to discuss with the agency and with other stakeholders. Thank you.

DR. DUBLIN: Thank you. I guess I would just emphasize that we also know from many other areas of attempting to improve clinical practice and bring about provider and patient education, that if you want a standardized set of information delivered in a standardized way, healthcare providers are not always the best people to task with that. As a primary care physician, I recognize the idiosyncrasies and inconsistencies between providers, and I guess I would just highlight the value of really considering an alternative approach that takes the provider out of the equation. Thank you. That's the end of my questions for this topic.

DR. LO RE: Dr. Rasmussen, your hand is up

next.

DR. RASMUSSEN: Yes. I had a couple of questions about the pregnancy registry for IPMG, I think for Dr. Ephross. The first is how is confidentiality assured for patients that are part of the pregnancy registry? I'm guessing with the changes in laws related to abortion, that women are going to be more reluctant to provide information if they can't be reassured of confidentiality to be part of the pregnancy registry.

Then I wondered about whether there'd been attempts to streamline the pregnancy registry information or whether that's something that we're going to be discussing today. I was thinking it was very easy for me to participate in CDC's V-safe program, where I could just answer -- they keep sending me texts, but it's easy enough to respond because it's just a few questions to answer regarding the registry, and so it's very easy to be part of a registry that way. Thanks.

MR. SHAMP: Jim Shamp from UBC. I will ask Dr. Ephross to respond.

Dr. Ephross?

DR. EPHROSS: Sara Ephross, Syneos Health.

Regarding your first question, Dr. Rasmussen, I think the issue of confidentiality is an important part of the patient experience here. I think that concerns about confidentiality may be a large part of patients' reluctance to give registry consent, as well as to give an authorization to contact their individual healthcare providers.

In terms of the second question, I think that is something that we're going to be discussing later today, and the IPMG is keen to work with FDA and the advisory committee to help understand how to make this easier to get high-quality data. Thank you.

DR. RASMUSSEN: Thank you.

DR. LO RE: Great. Thank you.

Dr. Green, your hand is up.

DR. GREEN: Hi. Thank you. Can you guys see me?

DR. LO RE: Yes.

DR. GREEN: Okay. Great.

The question, since we were looking for data, is I would like to know if there is any -- if you look at pregnancies reported prior to COVID when not as many people were doing home pregnancy tests, and telemedicine, and things along those lines, to when COVID happened and now those things were relaxed and you can do home pregnancy tests, is there any data on how many pregnancies were reported in people who were doing home pregnancy tests versus people who were doing CLIA-certified labs pregnancy tests?

The reason I ask is the pregnancy rates seem to stay very similar, and if truly doing a home pregnancy test was causing a lot of issues, I would expect to see those numbers go up, particularly, if you parse it out, in people who are doing home pregnancy tests versus going to a lab.

My other question is, with the sharing of the medication as a concern, my question really is, I thought the proposal was we do it in the beginning, and then we have to counsel them again

at 120 days, because what it sounds like is we'll have to have appointments for people to come in specifically to say, "Yes, you must not share this medicine every month." We're talking about decreasing burdens on patients. I feel like that's bringing in patients and running up charges for no real benefit. Over.

DR. LO RE: Thanks.

MR. SHAMP: Jim Shamp from UBC. To address your first question, the iPLEDGE REMS system did not collect the actual source of the pregnancy tests during the public health emergency, so we don't have specific data indicating the pregnancy tests and whether or not those patients were pregnant and caused an increase in the pregnancies. I will ask Dr. Greg Wedin to address your second question about the counseling for the 120-day confirmation interval.

Dr. Wedin?

DR. WEDIN: Greg Wedin, Upsher-Smith Laboratories. The counseling with each monthly prescription, as we think about that, it's

important to remember that the limit on prescriptions for isotretinoin is 30 days, and that really should not change. So there needs to be an interaction between the prescriber and the patient in order to determine, is isotretinoin therapy necessary? Should it continue? Should the dose be the same? Should we increase or decrease the dose?

All of those sorts of interactions need to take place on a monthly basis since prescriptions are required monthly, and it's during that period of time we believe that counseling on the safe-use conditions can take place. And as I mentioned earlier, certainly telemedicine is an acceptable approach to providing that sort of counseling so that actual in-office visits are not needed for that patient population. Thank you.

DR. LO RE: Great.

Dr. Green, any follow-up?

DR. GREEN: No. Sorry, no follow-up. I think this is an item for discussion later anyway, the necessity of this kind of thing, and it's a potential vote later, so I will hold off on

anything until that point.

DR. LO RE: Okay.

Dr. Tollefson?

DR. TOLLEFSON: Thank you. My question has to do with the 19-day lockout period after the initial report. I recall that there were 12 reported pregnancies over a 5-year reporting period in that 19 days. I understand that there might have been more than that that were not reported, but if you look at those ones that were reported, were you able to break down at what stage those pregnancies occurred? Because we got data that a certain percentage of pregnancies are detected at 10 days, at 14 days, at 19 days, so is there a period of time in there where more of the pregnancies were reported?

MR. SHAMP: Jim Shamp from UBC. From years 12 through 17, there were 12 pregnancies reported after that 19-day wait, and you are correct that these are not required to be reported because they are not exposed, so it's possible that they are underreported.

We do not have any data available as to the specific timing of that pregnancy, but it is just further evidence that the program is working, and that we have detected these 12 pregnancies and prevented exposure to isotretinoin in the fetus. Thank you.

DR. TOLLEFSON: Thank you. I think my only comment is it might be helpful to have that information as we think about that time period.

DR. LO RE: Great.

Dr. Delost, your hand's up.

DR. DELOST: Yes. Thank you. Based on that comparative lack of data on drug sharing, and you are pretty firm with that 30-day supply from what I understand -- but from a patient burden and a prescriber burden standpoint, and the way the prescriptions work most of the time, without that drug sharing data and the fact that you could follow up at 90 days instead of 120 days, I would propose maybe considering that 90-day medications with 90-day follow-ups would match up with the way our payers pay or with the community pharmacy for a

90-day supply; and lacking any more severity as far as the data, the drug sharing, we could still achieve all that itself.

The only problem would be is to change some RMA requirements because with the RMA, we'd have to know when those RMAs are done and when to reassess the system as far as payment for the follow-ups on 90 days. So we have to look at that whole system, but just a proposal, probably premature, but maybe IPMG or FDA will approach this subject. It might be premature, but if you want to talk about it, it'd be great. Thank you very much.

MR. SHAMP: Jim Shamp from UBC. I just want to clarify my response earlier about the sharing of the drug. I believe the question was specific to patients that became pregnant, where we knew the drug was shared. We do have data on specific sharing of medications. Through the life of the program, there have been 24 reported instances of drug being shared. Most recently in years 12 through 16, we have had 4 cases of drug being shared, and it's important to understand in

this that these are retrospective reports of the drug sharing. Thank you.

DR. DELOST: Just to clarify, I hope I addressed this just for the person that's not able to become pregnant. I want to make sure we address that. That's the only group I'm looking at.

MR. SHAMP: Yes, understood.

Jim Shamp from UBC. The data we have of these 24 instances throughout the years, we don't have it broken down at this time by specific types of patient categories, but of the four documented cases recently, we had one case in year 14, where it was a 19-year-old male that shared drug; two cases in year 13, both again male; and then in year 12, we had one case where it was an 18-year-old male patient that shared drug with another person. Thank you.

If I can just also add that we do believe these numbers of the sharing of the drug are underreported because they are only spontaneous reports. Thank you.

DR. LO RE: Great. Thank you.

DR. DELOST: Thank you.

DR. LO RE: Dr. Delost, any other questions?

DR. DELOST: No, not at this time. It took me a while to unmute there.

DR. LO RE: Thank you.

Dr. Salvas?

DR. SALVAS: Thank you. Brian Salvas from CVS Health.

Three questions. The first is around health equity and how might we consider disparate outcomes by demographics as part of our evaluation of the effectiveness of this program. It seems like from the data that's been shared, we have a very effective program, but I do wonder about the folks that were not necessarily helping.

Question number two is about technology enablement, and the call center data sort of triggered this for me. How might improved technology improve the provider, patient, pharmacy experience? I'm thinking about highly effective self-service tools in the digital age that we're in.

Then third, related to the survey shared earlier on the evaluation of the effectiveness of the program, particularly the question around pharmacists understanding the distribution guardrails of these products, has IPMG considered the central nature of REMS compliance for larger players like myself, which are very common in the chain drug world, and potentially changing the way that they're looking to assess that sort of performance.

MR. SHAMP: Jim Shamp from UBC. To address your first question about the health equity, the iPLEDGE REMS does not restrict a prescriber's or pharmacy's participation in the REMS. That is up to them to participate, so we have no restrictions on any sort of location, so I don't think we can provide any additional information on that.

On your question about the technology, if you could expand for me to help me understand a little bit your comment about self-service tools. Can you give me an idea of what you're talking about, please?

DR. SALVAS: Sure. I would imagine a world where we would likely not want to have anyone reaching out to a call center. That would sort of be a North Star, at least for me. So I'm curious. Are there additional opportunities to leverage digital tools to help enable improved experience that solve for some of the patient and provider friction points?

MR. SHAMP: We certainly do have the ability to do some self-service on the website. All the functionality of the REMS is available on the website as well, so there is not a need to call a call center. You can do everything on the website. Specific self-service things such as password reset are also available, so there is some of that available today, and we'd certainly appreciate any suggestions that we could further discuss with the agency and stakeholders on that.

Then on your pharmacy understanding, if you could just clarify your question. I didn't quite understand what your question is.

DR. SALVAS: There was one particular

question in the REMS program brief provided earlier this morning related to survey questions provided two different provider groups to gauge provider understanding of key program elements. One of those questions was related to the pharmacists understanding some of the guardrails around only procuring from enrolled distributors and things like that.

In a world that we practice in, a lot of that activity is not being housed within the actual pharmacy itself. It's being handled centrally, so to me it explains the potential gap that a bench pharmacist may have in understanding those program elements. So I'm just curious. Assuming that this is a benchmark that you're going to want to continue to go after, are there other ways to get the appropriate signal there without having to compromise our understanding of how the programs work?

MR. SHAMP: Yes. Jim Shamp from UBC. If we can have slide up, please?

I think this is the slide you were referring

to, and specifically, the key risk message specific to how isotretinoin product should be obtained from a registered wholesaler and not be shared. So you provide an interesting thought and idea. This is part of the knowledge assessment and behavior survey that is conducted as part of the iPLEDGE REMS assessment, and we do out -- and this is all done confidentially. We don't know who the responders are. But I think what you're suggesting here is that perhaps we should not be contacting necessarily -- I think you refer to them as the bench pharmacists, but perhaps to something more centralized.

Am I understanding your thought correctly?

DR. GREEN: That's where I'm going to, where essentially, particularly for many of the larger chain players, these sorts of activities in compliant to the REM program guardrails are happening outside of the four walls of any individual pharmacy.

MR. SHAMP: Again, we appreciate that thinking, it's an interesting idea, and we'd be

happy to discuss this and another ideas around this with the agency and stakeholders. Thank you.

DR. GREEN: Thank you.

One last clarifying question on the health equity piece, I understand every pharmacy can enroll and any provider can enroll. I guess where I'm going is, are the elements of the program itself -- they seem to be delivering appropriate outcomes based off of the guiding principles of the program to eliminate fetal exposure to this particular drug, but I am curious if we understand there are different populations that may be disproportionately impacted by some of the mechanics of this in terms of not getting access that we should be potentially considering as we ponder future changes to the program.

MR. SHAMP: Jim Shamp from UBC. We don't have any data to answer that specific question, but what we do know is that many of these mechanics of the REMS are actually in the labeling themselves, so they're not specific to the REMS. They are requirements that come out of the labeling. So

those requirements would exist whether you had the REMS or not.

DR. GREEN: Okay. Thank you.

DR. LO RE: Dr. Huybrechts?

DR. HUYBRECHTS: This is Krista Huybrechts, and I have a question for IPMG. I think I might have misunderstood something, so I was just hoping to clarify. It relates to, again, dropping the requirement for the monthly documentation of the counseling for patients who can't become pregnant.

As you were discussing the benefits and the potential disadvantages of the benefits being the lesser burden, I thought that with one of the potential risks, you mentioned that they could now potentially then get their prescription from different providers, different prescribers. If I understood that correctly, I was hoping whether you could clarify how that would happen in the sense that they still need to go back to their provider monthly to get their new prescription.

So I was just wondering how would the mechanism work that they would now be able to get

prescriptions from different providers, if I understood it correctly.

MR. SHAMP: Jim Shamp from UBC. I will ask Dr. Wedin to respond to this question. First, I just want to clarify. I'm not sure if I just didn't hear you right. This proposal is specific to patients who cannot become pregnant.

DR. HUYBRECHTS: Yes.

MR. SHAMP: Dr. Wedin?

DR. WEDIN: Greg Wedin, Upsher-Smith Laboratories. The concern we have is under the proposed modification to change the required interval or documenting confirmation every 120 days is there's a period of time there where the patient will receive several prescriptions or may potentially receive several prescriptions. It is possible, for example, that a patient after that initial confirmation by the certified prescriber, that after a month, the patient may decide that maybe there's an easier way to get the prescription filled.

Perhaps their primary care provider is

someone they would turn to, and say, "I saw the dermatologist. They started me on isotretinoin. They said I would need to be on therapy for perhaps 3, or 4, or 5 months, and rather than having to visit the dermatologist, could I receive a prescription from you?" That prescriber may not be enrolled in the REMS program. They may not understand the risks or the requirements of the program. But if that prescriber were to provide a prescription to the patient, or send a prescription to the pharmacy, the pharmacy wouldn't detect that, and the prescription could be dispensed without the knowledge of the certified prescriber who started the patient on isotretinoin. So that's one of the primary concerns.

DR. HUYBRECHTS: Could I ask you a quick follow-up question? In the example you gave, the primary care provider would still have to register with the REMS system before he or she could issue the prescription, right? So if that is the case, are you saying that at the iPLEDGE level, it can be detected that it's basically the same patient

getting prescriptions from two different providers that are registered with the system?

MR. SHAMP: Jim Shamp from UBC. If I could try to add something here that might help clarify the situation. Right now, the way the system works with the monthly confirmation, that monthly confirmation has to be performed by a certified prescriber. So in order to get drug today, you have to be confirmed, which provides a one-to-one linkage between the confirmation by a certified prescriber to the dispensing.

If we move the confirmation interval out to once every 120 days, the subsequent authorizations for that patient after that initial one will no longer have that one-for-one link to a certified prescriber. So in that case, any prescriber could be writing that prescription, and we no longer know for those intervals that the patient is under the care of a certified prescriber.

DR. HUYBRECHTS: Thank you. That is helpful. No further questions for my end.

DR. LO RE: Thank you.

Dr. Cowen, you have your hand up.

DR. COWEN: Thank you. I'd like to circle back to one of the earlier comments about burden of doing a home pregnancy test, as that would relate to what was done during the pandemic, and make the comment that I think it's important that we are forward thinking in terms of several people have mentioned telemedicine, and this sort of acne specific follow-up in particular is very well suited to the digital platform.

So certainly the suggestion to do urine pregnancy tests when patients are in the office would be very reasonable, but I would like to see the data for patients, and often parents, and whether or not it's really considered a burden to do a urine pregnancy test at home compared to going to a dedicated lab. Most dermatology offices don't have labs, so it's a second visit with the child often taken out of school and parents taking off work to do this. So I think that question of reducing burden and then thinking about in-office visits versus things that can be done digitally is

something that I would encourage the group to think about.

MR. SHAMP: Jim Shamp from UBC. As far as telemedicine goes, the sponsors are aligned with the use of telemedicine, provided all of the elements to assure safe use and conditions are met for that. And you heard Dr. Wedin state earlier that we'd certainly be interested in studying data that would show us whether or not the home pregnancy tests could actually reduce burden and continue to be safe and help us to prevent the fetal exposure to isotretinoin. Thank you.

DR. COWEN: Thank you.

DR. LO RE: Dr. Dublin?

DR. DUBLIN: Thank you. I just wanted to follow up on a comment made by Dr. Wedin that the provider is already interacting with the patient every month when the patient is requesting their refill. I was wondering if any of the dermatologists on the committee could speak to the clinical necessity of how frequent a follow-up is recommended to check whether the patient is

tolerating the prescription and whether you need to adjust the dose.

Is that something that would typically happen on an every 30-day cadence?

DR. LO RE: Dr. Katz wants to respond.

DR. KATZ: In my own practice, 30 days would be a good interval. There was a comment about a 90-day prescription previously, and I think just from a clinical perspective, in my practice, that would not be what I would be interested in. There are too many potential side effects and also questions about effectiveness that I'd want to check in every 30 days.

DR. DUBLIN: Thank you. That's extremely helpful.

I had a comment or question about the health equity issue. I think there were a number of comments from patients in the public comments indicating the need to go anywhere -- whether it's your physician's office or a lab -- to do the pregnancy test was difficult, especially for people who were working and had children they needed to

care for.

So I just want us to realize, again, this health equity issue, to me it's about the patients who drop out of the system, so a way to look at it is I know you would have to collect data on things like race, or ethnicity, or socioeconomic status, but I do think that there's a disproportionate burden placed on people who don't have jobs, or they can't easily miss work, or who work long hours who can't afford transportation, and we should consider that. Thank you. I'm done with my question.

DR. LO RE: Thank you.

Mr. Shamp, did you want to comment?

MR. SHAMP: Yes. Jim Shamp from UBC. It is important to understand and appreciate the situations of certain patients, and the sponsors certainly appreciate that, but because the issue here of the fetal exposure to isotretinoin is so significant and serious, we do have to balance the burden of these safe-use conditions against the goals of the REMS. Thank you.

DR. LO RE: I have 1:00. We're going to take a 30-minute lunch break. I'm going to note we have two -- Dr. Liu and Dr. Hernandez-Diaz -- who have their questions up. We'll start with them when we come back.

Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We're going to reconvene promptly at 1:30 p.m. Eastern Daylight Time. Thanks.

(Whereupon, at 1:00 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

DR. LO RE: Alright. We are going to resume, but we have one final presentation at 1:30, now, from Dr. Crist of the FDA, and then we will resume clarifying questions.

FDA Presentation - Lindsey Crist

DR. CRIST: Thank you, Dr. Lo Re.

Good afternoon. My name is Lindsey Crist, and I'm a risk management analyst in the Division of Risk Management in the Office of Surveillance and Epidemiology in CDER, at the FDA. I'm speaking today on behalf of the agency's iPLEDGE review team, which is a multidisciplinary team with subject matter experts on REMS, dermatology, maternal health, as well as other disciplines to provide recommendations on potential modifications to the iPLEDGE REMS.

This presentation will provide the committee with the approach and results from the FDA review team's evaluation of the iPLEDGE REMS, and share our analysis of the REMS requirements and potential

modifications that may minimize burden without impacting safety. The presentation will conclude with a summary of topics for which we seek committee discussion and advice.

Risk evaluation mitigation strategies, or REMS, are drug safety programs required for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. Risk mitigation tools and interventions are utilized to reinforce necessary medication-use behaviors and actions that support the safe use of a medication. The required interventions inherently impose burden on the healthcare system and may create unintended barriers to patient access.

In the context of a REMS, burden reflects the additional effort that healthcare professionals and other stakeholders, such as pharmacies and patients, expend in complying with REMS requirements. Risk mitigation will always involve some degree of burden to achieve the goal of safe use of a medication.

REMS-related burden can potentially impact the healthcare system and its stakeholders. There could be prescribing preferences for therapies without a REMS. Prescribers and pharmacists may be required to work outside of their typical workflow or systems. More administrative time, resources, and staff may be necessary to complete requirements, and there may be barriers to patient access leading to treatment delays or interruptions. Risk mitigation involves a continual process that includes program assessment and modifications or changes when needed. The agency seeks to minimize burden and prevent unintended access issues whenever possible for REMS.

This meeting provides an opportunity to consider changes to the iPLEDGE REMS to improve efficiency and minimize burden without compromising the safe-use goals of the REMS. The review team completed a systematic evaluation of all iPLEDGE elements to assure safe use and requirements. The purpose was to assess the requirements for all

participants and consider if there were any opportunities to modify the REMS to minimize burden, to the extent possible, without impacting safe use of isotretinoin.

Although all requirements for all participants were evaluated, the review team focused the analysis on requirements that may contribute to stakeholder burden, cause unintended patient access issues, or cause treatment gaps and delays. Although the iPLEDGE REMS was described in detail, the next few slides are intended to help focus as we shift to discussing the approved REMS requirements, the review team's analysis, and the proposed changes.

The goals of the REMS are to prevent fetal exposure to isotretinoin and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-use conditions. It is important to keep these goals at the forefront when considering any changes to the REMS.

Given the goal of preventing fetal exposure, prescribers must assess the reproductive potential

of patients prior to starting therapy and assign the appropriate patient risk category. The REMS modification, approved in October 2021, updated the patient risk categories from three into two categories that utilize gender-neutral language throughout the REMS. The intent was to remove barriers to patient access and create a more inclusive REMS.

There are now two categories. The first category is patients who can become pregnant. This includes cisgender females and transgender males. The second category is patients who cannot become pregnant. This includes cisgender males, cisgender females, and transgender males who have undergone a hysterectomy, bilateral oophorectomy, or who are postmenopausal; and transgender females.

Assessment of the appropriate risk category is completed by the prescriber at enrollment and documented on the patient enrollment form. It should be reassessed throughout the treatment course and for any future courses. The assigned risk category must be accurate, as the REMS

requirements differ based on the category.

This slide represents a high-level overview of the iPLEDGE REMS, its key stakeholders, and requirements. The iPLEDGE REMS is a web-based, centralized system that requires participation and enrollment of prescribers, patients, pharmacies, and wholesalers to ensure safe use and to achieve the program goals. Prescribers and pharmacies must be certified and attest to understanding the REMS requirements. The iPLEDGE REMS links completion of REMS requirements to dispensing. Pharmacies must obtain authorization, known as the risk management authorization, or RMA, prior to each dispense of isotretinoin for all patients, regardless of patient risk category.

There are specific safe-use requirements for patients who can become pregnant, outlined here in purple on the left side, and for patients who cannot become pregnant, outlined in teal on the right side. The timing of requirements spans from before treatment, during treatment, which typically lasts about 15 to 20 weeks, as well as after the

treatment course ends. Note that the requirements for patients who can become pregnant are more extensive given that these patients have a direct risk of fetal exposure. The REMS requires pregnancy testing and actions within iPLEDGE by both the prescriber and the patient. Patients who cannot get pregnant are enrolled and get counseled monthly but are not required to interact with the iPLEDGE system each month.

Isotretinoin may not be dispensed without verification that all safe-use requirements are met. When a pharmacist receives a prescription, they must access iPLEDGE to obtain authorization to dispense. The risk management authorization, or RMA, is a unique number generated by the REMS that verifies that all safe-use requirements are met, and isotretinoin may be dispensed.

Depending on the patient risk category, there are several safe-use requirements that must be completed each month by the prescriber or patient. If any of the requirements are not met, the RMA will be denied. If more than one

requirement is not verified, there may be multiple denials. An RMA denial may result in potential delays in therapy, depending on the time necessary to complete the requirements; however, the prescription may ultimately be authorized and dispensed without delay when evidence of missing requirements is documented.

The presentation will provide the review team's analysis on select requirements from the iPLEDGE REMS. First, we will review the current REMS requirement, discuss the relevant background information to provide context, and summarize our recommendations with rationale. For certain topics, we will highlight where we seek the committee's advice and considerations for discussion.

The first REMS topic is the patient enrollment requirement. iPLEDGE requires all patients to be enrolled in the REMS regardless of their assigned patient risk category. The review team recommends that all patients should continue to be enrolled in the REMS and complete

requirements prior to initiation regardless of the risk category.

Enrollment of all patients, including patients who cannot get pregnant, ensures that prescribers are required to assess and document the patient risk category within iPLEDGE at treatment initiation and throughout therapy if there are changes. It is imperative that the risk category is accurate, as the REMS requirements differ based on the category, and it is important to ensure the appropriate safe-use requirements are applied.

Another aspect to consider is from the perspective of the pharmacy. Pharmacists cannot determine patient risk categories based on a patient name on a prescription or the perceived sex when a person presents to the pharmacy. Enrollment of all patients results in a single process for pharmacy dispensing without having to establish different policies and procedures based on the patient category. Changes to this process could increase burden on pharmacies and lead to confusion, as pharmacists must work outside of the

typical workflow to access iPLEDGE and obtain authorization for each prescription.

The next topic relates to limiting the prescription days' supply. A maximum of 30-day supply with no refills may be prescribed and dispensed. The review team recommends isotretinoin prescriptions continue to be limited to a 30-day supply for all patients. The 30-day supply limit ensures that patients are required to be evaluated by a prescriber on a monthly basis and ensures that safe-use requirements are verified each month.

Limiting the supply should also minimize leftover or unused medication that the patient could use at a later time without being under the care of a prescriber or could share with friends or family members. A range of 1-to-8 pregnancies each year were attributed to a person taking leftover or unused medication.

In iPLEDGE, all patients are required to be counseled by prescribers on the risks of isotretinoin and the REMS requirements at treatment initiation and monthly throughout therapy. For

patients who can become pregnant, patients are also counseled on contraception options by their prescriber or are referred for contraception counseling. Prescribers are required to document that counseling was completed each month. This administrative step is referred to as confirmation of counseling, and it involves the prescriber or a designee on behalf of the prescriber accessing the iPLEDGE system and documenting that counseling was completed.

For patients who can become pregnant, this counseling confirmation step is only one component of the required prescriber documentation. Prescribers are also required to document the pregnancy test results and the patient's selected contraception methods each month.

A screenshot of the prescriber view for confirmation of counseling is shown here. The prescriber is asked to select a box confirming that they have counseled the patient and that the patient understands and is capable of complying with the requirements; however, additional

prescriber documentation is necessary before the patient, who can become pregnant, is eligible to receive isotretinoin.

This screenshot depicts the prescriber view of the remainder of prescriber documentation required for patients who can become pregnant. It includes entering the patient's contraception methods each month via the dropdown box, the pregnancy test results, and the relevant diagnosis; that is whether the patient is pregnant or not.

After consideration of the confirmation of counseling requirement, the review team recommends maintaining the monthly prescriber documentation of counseling in iPLEDGE for patients who can get pregnant. As described, this is only one component of the required prescriber documentation for this patient category, and it does not result in a significant amount of additional burden for prescribers. Regular reminders to counsel support the goal of informing patients on the safety risks and requirements. From a patient access perspective, prescribers failing to complete this

confirmation of counseling step represents only 11-to-14 percent of RMA denials for this patient risk category.

As described, all patients, including patients who cannot get pregnant, are required to be counseled. As a requirement of the REMS, patients who cannot become pregnant are counseled on the risks of isotretinoin and the need to avoid sharing medication or donating blood, as this could result in fetal exposure. Prescribers must document this counseling in the iPLEDGE monthly.

This website screenshot shows the prescriber view of confirmation of counseling for patients who cannot get pregnant. Of note, only the prescriber is required to interact with the iPLEDGE REMS on a monthly basis. Once this step is complete, patients who cannot become pregnant are considered eligible to receive isotretinoin. Patients who cannot get pregnant do not need to complete additional steps or interact with the iPLEDGE monthly before obtaining their prescription.

After consideration of the confirmation of

counseling requirement for patients who cannot become pregnant, the review team determined that monthly documentation of counseling was not necessary. We seek advice from the committee on the option to extend the interval for documentation; for example, to every 120 days, as proposed by the IPMG, or whether documentation of counseling at enrollment is sufficient and that the monthly documentation requirement could be removed.

As described, this as an administrative step that requires prescribers or designees to move out of their typical workflows to access iPLEDGE and check a box to document that counseling was done, counseling on the risks of isotretinoin and the importance of not sharing medication or donating blood. In addition, counseling for other risks not included in the REMS should still occur monthly by prescribers, but given that this patient risk category is not directly at risk for fetal exposure, removal of this documentation step can minimize administrative burden without impacting safe use of isotretinoin.

When considering patient access, failure to complete this documentation step is the most common reason for RMA denials for patients who cannot become pregnant. By removing or extending the interval, it could eliminate up to 78 percent of RMA denials for patients who cannot become pregnant. This could reduce calls from pharmacists to prescribers to resolve the denial and may lead to a reduction in treatment delays or gaps for this patient risk category.

The presentation will now focus on the requirements that only impact patients who can become pregnant. Appropriate contraception is an important tool to prevent pregnancy during the course of therapy. iPLEDGE requires patients who can become pregnant to use two forms of contraception consistently, starting at least 30 days prior to treatment initiation, throughout treatment, and for 30 days after treatment.

The iPLEDGE REMS specifies the appropriate contraception methods patients may select while on therapy. Patients are counseled on options and are

required to select a primary method and a secondary method. iPLEDGE does allow patients who can become pregnant to commit to continuous abstinence as a lifestyle choice, and this is defined as not having sexual contact with a partner that could result in pregnancy.

Contraception choice is patient dependent and based on a variety of factors. Abstinence is consistently in the top two choices. The most common contraception choices are consistently birth control pills as the primary form, and male condoms is the secondary form. As our maternal health expert presented earlier, these are user dependent and have more potential for imperfect use. Despite requiring two forms of contraception, the most common reasons cited by prescribers for unintended pregnancy were not using two forms of contraception, contraceptive failure, and unsuccessful abstinence. Given the contraception failure rates, the data on the top contraception choices by patients in this program, and the typical length of therapy of only 15 to 20 weeks,

we are not recommending changes to this requirement at this time.

One of the steps in the prescription authorization process each month for patients who can become pregnant is that the prescriber and patient enter the patient's two forms of contraception into the iPLEDGE system or document the patient's commitment to abstinence. The primary form of contraception selected by the prescriber must match the patient's choice. If the primary forms do not match, the RMA will be denied, and the prescription cannot be authorized until the mismatch is resolved.

Although documenting contraception methods and requiring alignment each month may be perceived as an administrative burden, this requirement promotes continued communication regarding the importance of contraception, as well as re-evaluation of contraception choices between the prescriber and patient throughout therapy. It facilitates discussion related to possible changes in contraception to a new choice and is also a way

to reassess the patient's commitment to abstinence.

The review team recommends maintaining this requirement. We consider data from assessment reports on the reasons for unintended pregnancy. In addition, since prescribers and patients interact with iPLEDGE monthly, for other requirements, this step does not result in increased burden on prescribers or patients.

This slide provides a visual overview of the required pregnancy tests for isotretinoin. The stars represent required pregnancy tests over a time line that is not to scale but is intended to highlight the testing requirements prior to treatment, during treatment, and after treatment.

Prior to starting isotretinoin, patients who can become pregnant must have two negative urine or serum pregnancy tests. The first test is a screening test, and it is completed at the time of enrollment. Patients may only be enrolled in the program if this first test is negative. At this time, the patient begins two forms of appropriate contraception at least 30 days prior to starting

therapy or commits to continuous absence.

A second test known as the confirmatory test is also required before starting isotretinoin, and this test must be performed in a CLIA-certified laboratory, and the interval between this test and the screening test must be at least 19 days. Labeling also specifies that for patients with regular menstrual cycles, the confirmatory test should be obtained within the first 5 days of the menstrual period. For patients without regular cycles, the confirmatory test should be completed immediately preceding the beginning of therapy.

Pregnancy tests are also required each month throughout therapy using a CLIA-certified laboratory so that a negative test is confirmed before dispensing. After a treatment course, two pregnancy tests are required, one at the end of treatment and an additional test one month later, as fetal risk persists for up to 30 days after discontinuation.

The iPLEDGE REMS requires pregnancy testing using a CLIA-certified laboratory. This

requirement was originally put in place to reduce the likelihood of laboratory error for pregnancy tests and to eliminate the possibility that a home pregnancy test would be ordered but not performed. The Clinical Laboratory Improvement Amendments of 1988 established quality standards for laboratory testing to ensure accuracy, reliability, and timeliness of results regardless of where a test was performed. The regulations and required certifications are based on test complexity, with more stringent requirements for more complex tests.

CLIA-waived tests are considered simple laboratory examinations and procedures that have an insignificant risk of an erroneous result when used according to the manufacturer instructions. Most urine pregnancy tests are intended for over-the-counter use and are CLIA-waived by regulation, which means that they are simple to use with low risk of erroneous results. These over-the-counter, CLIA-waived tests are designed for use by lay users and may be performed or used outside of a CLIA-certified laboratory; for

example, at a patient's home or in a provider's office.

The review team will provide our analysis on the following topics related to pregnancy testing, setting, and timing of pregnancy tests. The first topic related to pregnancy testing is on the requirement for the use of a CLIA-certified laboratory for the confirmatory pregnancy test and all subsequent tests.

Although the program requires testing using a CLIA-certified laboratory, this requirement results in additional burden for patients. Patients may be required to have a separate laboratory visit just for pregnancy testing, and this results in additional time and cost to the patient. This also adds complexity for completing all requirements within the designated 7-day window each month. The review team recommends removal of the requirement to only use a CLIA-certified laboratory for pregnancy tests. We recommend allowing pregnancy testing to be performed in a provider's office as an alternative.

Urine pregnancy tests are CLIA-waived by regulation and must meet specific performance criteria; therefore, safe use should not be impacted. Removal of this requirement should increase flexibility for patients by reducing the need for separate office and laboratory visits and may improve the patient's experience.

The COVID-19 public health emergency resulted in changes to the iPLEDGE requirements over the past three years to ensure access to isotretinoin therapy was maintained. Consistent with the agency's guidance regarding REMS requirements during the public health emergency, the iPLEDGE REMS allowed the use of home pregnancy tests to minimize potential access issues since patients needed flexibility due to self-isolation and quarantine policies.

At-home pregnancy testing was allowed as long as results were communicated to the prescriber. The process consisted of the following: the patient performs a pregnancy test at home using an over-the-counter test; the patient

communicates the pregnancy test result and date of the test to the prescriber; and then the prescriber enters the result and date into iPLEDGE per the usual process. No other changes were made to other requirements, such as the prescription window or contraception during the public health emergency.

The agency recognizes that there are potential benefits associated with home pregnancy testing, especially when utilized with telemedicine on the patient experience and associated time and costs with office visits, laboratory visits, and missed work. However, the review team does not recommend the continued use of home pregnancy testing beyond the public health emergency.

There is insufficient data to fully understand the extent of home pregnancy testing during the public health emergency. iPLEDGE collects pregnancy results; however, the system does not have a mechanism to collect where and how the test was performed; therefore, there are no available comprehensive data on how many of the required tests over the past three years were

completed outside of CLIA laboratories or using home tests.

Although the reported pregnancy rates are comparable to previous years, it is difficult to make conclusions without fully understanding the extent of home pregnancy test use. In addition, published literature of experiences during the public health emergency have identified non-compliance, including intentional falsification of results by patients.

One study at an academic medical center reviewed the medical records of 89 patients who used home pregnancy tests while taking isotretinoin during the public health emergency. It found that 15.7 percent of patients submitted falsified pregnancy test results. Examples of falsification included the use of stock images from the internet, repeated use of the same pregnancy test result, and editing previous test images. An additional case series of 7 patients was published at another center, demonstrating falsification of tests as a potential safety issue.

Though there are benefits of home pregnancy testing, we do not have sufficient evidence in whether home pregnancy testing impacts the safe use of isotretinoin. The review team does not recommend continued home testing at this time; however, we seek additional committee discussion and advice on this topic.

iPLEDGE requires that patients who can become pregnant complete all safe-use requirements and obtain the prescription within a 7-day prescription window, starting from the day the pregnancy test is performed. This window is a finite time period, and if requirements are not complete or if the patient fails to pick up the prescription on time, the prescription is no longer valid, and the process must be restarted, including repeating a new pregnancy test. Patients cannot have an unlimited pickup time, as it is important to have a negative pregnancy test result in close proximity prior to each dispense for the safe use of isotretinoin.

Concerns have been raised about the

challenges of completing all requirements in obtaining the prescription within the 7-day window, especially with the first prescription. This involves coordination of office visits, laboratory visits, and completion of prescriber documentation, patient comprehension testing, as well as allowing time for pharmacy dispensing and patient pick up. However, the IPMG has provided data that show the median time for picking up the first prescription is 2 days -- that is on day 2 of the prescription window -- and the mean ranged from 2.31 to 2.44 days.

Data also show that 80-to-85 percent of patients who can become pregnant are able to pick up the first prescription within the 7-day window. Based on this data and the need to ensure that patients are not pregnant prior to dispensing, the review team recommends to maintain the 7-day prescription window.

iPLEDGE requires that patients who can become pregnant enter a 19-day lockout -- this is also referred to as the 19-day wait period -- if

the first prescription is not picked up or obtained within the first 7-day window. The 19-day lockout has garnered much attention and confusion. It causes a delay in treatment initiation, which results in patient's frustration, additional time, as well as costs. This slide provides a visual to better understand the 19-day lockout and time frames.

As you can see, the stars reflect pregnancy tests and the gray bar reflects time. iPLEDGE requires that patients who can become pregnant pick up their prescription within the 7-day window. This window begins on the date that the confirmatory pregnancy test specimen was collected. During the window, patients and prescribers complete the safety requirements and the pharmacy is required to obtain authorization and dispense prior to the end of the window.

If requirements are not complete, or the patient does not obtain the medication within this time frame for the first window, the patient will enter the 19-day lockout or the 19-day wait period.

This means the patient must wait 19 days from the date of the confirmatory pregnancy test prior to repeating a new test and completing the other requirements to open a new prescription window.

It is important to understand that this 19-day lockout for missing the window only applies to the first prescription. It is intended as an additional layer of screening to detect pregnancy and prevent exposure to isotretinoin. For subsequent months, there is no waiting period, and the patient may restart the process to obtain a new prescription immediately.

The review team recognizes the importance of evaluating the 19-day lockout requirement, as it can result in a delay for starting isotretinoin therapy for patients who can become pregnant. We also recognize the importance of requirements that ensure patients are not pregnant prior to starting treatment with a teratogen. The review team seeks advice from the committee on whether to retain or change the 19-day lockout, given the goal of the program is to prevent fetal exposure to

isotretinoin.

There are a few important considerations when determining the need for a 19-day lockout. It is intended to prevent pregnancy exposure when there is a delay in obtaining the prescription, as it is important to have an accurate pregnancy test result before starting therapy. This period is the last opportunity to detect pregnancy and prevent exposure. At least 12 pregnancies have been identified during the 19-day lockout, from March 2017 through September 2022. Since patients have not started isotretinoin, this is likely to be an underestimate, as some patients may not report the pregnancy or may not return to restart the process for isotretinoin therapy.

When evaluating this requirement, the team also considered the impact on patient access. Supplemental data from the IPMG report that 15-to-20 percent of patients who can become pregnant miss the first 7-day window and enter this lockout; 170, 311 people entered the 19-day lockout, resulting in a delay to starting therapy.

This represents about 15.6 percent of the total patients who can become pregnant who obtained at least one RMA.

The 19-day lockout is intended as an additional layer of screening to detect pregnancy, and it is the last opportunity to prevent exposure before treatment is started. However, as discussed by my maternal health colleague earlier this morning, there is a delay from conception to when a pregnancy is detectable; therefore, there will always be the potential to miss pregnancies if conception occurs close to initiation of treatment. We acknowledge the importance of striking an appropriate balance between safety and the impact these requirements may have on treatment delays and patient access.

The last pregnancy testing topic is the requirement for post-treatment pregnancy tests. Post-treatment pregnancy tests consist of a pregnancy test at the end of treatment and 30 days later. The review team recommends maintaining post-treatment pregnancy tests since the risks

associated with fetal exposure remain for up to a month after completion of a course of therapy.

Although assessment data show high knowledge of the need for pregnancy testing after treatment ends, many patients do not complete these tests. Approximately 14 percent of patients were marked by their prescriber in iPLEDGE as having completed either the first or second post-treatment pregnancy test, and only 5.36 percent were marked as completing both post-treatment pregnancy tests. These are important tests given the persistent risk of fetal exposure; however, it is difficult to incentivize patients to return for these tests, as patients no longer need medication, and these visits result in additional time commitments and costs.

Despite the recommendation to continue contraception or abstinence for at least 30 days after treatment ends, pregnancies are still reported during this period. From March 2021 through December 2021, 16 of the 184 total pregnancies reported occurred within 30 days of

stopping isotretinoin therapy. Given the rates of non-compliance with post-treatment testing, this may be an underestimate of the actual pregnancies in this time frame.

iPLEDGE is required to maintain a centralized pregnancy registry for patients who become pregnant. Pregnancies may be reported to the registry, the REMS call center, or may be identified by a positive pregnancy test result entered into the iPLEDGE REMS system. All reports of pregnancy are investigated; however, patient and healthcare provider participation in the registry is voluntary and requires consent.

The pregnancy registry objectives include the following: first, to determine isotretinoin exposure status for each reported pregnancy; second, to document the outcome of each isotretinoin exposed pregnancy; and third, to determine, document, and analyze causes contributing to fetal exposure, a root cause analysis.

The pregnancy registry collects data from

the iPLEDGE system and through interviews of the patient and provider, if they provide consent. A questionnaire is used to conduct the root cause analysis interviews for pregnancies that occur. Data collection includes an initial interview follow-up at 30 days, as well as each trimester; outcome of the pregnancy and data; and any live births with follow-up for up to 1 year of age for the infant.

The review team considered the pregnancy registry objectives when evaluating this requirement and the data the registry provides. We determined that pregnancy exposure data is valuable for continued assessment to track pregnancies over time. This metric is important given the goal of the REMS is to prevent fetal exposure. Tracking pregnancy exposure rates is also important to evaluate the impact of any REMS modifications. In addition, the root cause analysis is helpful to identify contributing factors to pregnancy exposure and possible areas of improvement for the REMS. The registry goal also includes documentation of

pregnancy outcomes and fetal outcomes, if applicable.

Isotretinoin is a well-known teratogen, and there is extensive knowledge about its teratogenic effects. Continued collection of pregnancy outcome data is limited and may not be adding much to the current knowledge. In addition, patient privacy concerns regarding outcome data may impact participation. We seek committee advice on ways to streamline the pregnancy registry to encourage more participation to yield high-quality data, and in particular, whether pregnancy and infant outcome data collection continues to be necessary.

This concludes the iPLEDGE review team's analysis of the REMS and potential modifications to minimize burden without compromising safety. The team provided the following recommendations: to continue to require all patients be enrolled into iPLEDGE regardless of risk category and to maintain the 30-day supply limit for all prescriptions.

For patients who can become pregnant, the review team recommends maintaining the following

requirements: the monthly documentation of counseling; the contraception requirements; monthly documentation of contraception and alignment of the primary contraceptive forms between patients and prescribers; the 7-day prescription window; and post-treatment pregnancy tests. The review team recommends removing the requirement for only using a CLIA-certified laboratory and to allow the use of FDA-cleared pregnancy tests in a prescriber's office as an alternative.

The review team seeks additional advice from the committee on the following topics: for patients who cannot become pregnant, whether to extend the interval for prescriber documentation of counseling or remove the requirement to document counseling each month; for patients who can become pregnant, discussion on the use of home pregnancy testing beyond the public health emergency; whether to retain or change the 19-day lockout, also referred to by the IPMG as the 19-day waiting period, when the first prescription window is missed; and lastly, how the pregnancy registry

could be streamlined and whether collection of pregnancy and fetal outcome data continues to be necessary for a product with a well-established safety profile.

I want to take a moment to acknowledge the hard work of all members of the iPLEDGE review team for their expertise and assistance during the evaluation process, as well as in preparation for the meeting. Our references are outlined on this slide and the following. Thank you for the opportunity to provide our recommendations regarding the iPLEDGE REMS. We look forward to the committee's questions and discussion. Thank you.

Clarifying Questions to Presenters (continued)

DR. LO RE: Thank you, Dr. Crist; appreciate that presentation.

We're going to now take clarifying questions for the FDA. Please use the raise-hand icon to indicate if you have a question. Remember to lower your hand by clicking the raise-hand icon again after you have asked your question. Remember that when you're acknowledged, remember to state your

name for the record, direct your question to a specific presenter, if it's possible, and if you wish for a specific slide to be displayed, please let us know, and we'll put the slide up, if possible.

Finally, it would be helpful to me if you could acknowledge the end of your question with a thank you, or end of a follow-up question with, "That's all for my questions," so we can move on to the next panel members.

I want to be respectful to both Dr. Liu and Dr. Hernandez-Diaz because they had their hands up at the end of the last clarifying question section.

Dr. Liu, could I call on you first just because you had your hand up?

DR. LIU: That's fine.

This is Tao Liu. I have a question about the 19-day lockup. There are statistics that reports that during 2017 to 2022, there were 12 pregnancies, I would say unplanned or unexpected pregnancies, during the lockout period. During this time, this happened among 173,311 patients.

If divided by these two numbers, the pregnancy rates is about 0.07 per 1,000; so this is much lower than the general pregnancy rate for the iPLEDGE system, which is around 1 per 1,000 patients who can become pregnant.

If you look at this from the cost effectiveness perspective, the cost is we put this huge amount of effort to put this 19-day lockout for patients, for prescribers, and for pharmacists, and by the end, we only identify a small percentage of pregnancies, which is much lower than the entire iPLEDGE pregnancy rates. In this sense, this may not be cost effective.

My question is, if we look at it this way, do we think this actually creates an actual burden to all the stakeholders? Maybe this is something we need to consider, whether we still need the 19-day lockout. That's my question.

DR. LO RE: Dr. Liu, did you have a specific person you wanted to address that to? Is that the agency or IPMG?

DR. LIU: The FDA.

DR. LO RE: Dr. LaCivita, are you still taking questions for the agency at this time?

DR. LaCIVITA: Yes. Thank you.

That is a question that we have, the 19-day lockout. We are seeking feedback from the panel on that. We do understand that there is additional burden with a 19-day lockout, and I think you are correct; there are only a few pregnancies that are detected during that time period. However, they are detecting pregnancies, and it is the last opportunity to prevent fetal exposure.

I just want to see if Dr. Crist has anything to add to that.

DR. CRIST: Thank you, Dr. LaCivita. The only thing that I would like to add is that during that time period, there may be underreporting of pregnancies. Since the patient has not started the drug yet, we may not be capturing all the pregnancies in that time period.

DR. LaCIVITA: Thank you.

DR. LIU: Can I ask something? Even if we inflate this number by 10, this still is 0.6 per

1,000 patients. That's still less than 1 per 1,000 of the iPLEDGE system, so even underreporting is still much, much lower than the reporting of 1 per 1,000 pregnancy rate.

DR. LaCIVITA: This is Cynthia LaCivita from the FDA. Did you want me to take that question?

DR. LO RE: Sure, Dr. LaCivita.

Could you just clarify; what is the question, Dr. Liu?

DR. LIU: Yes. My question is -- I'm referring to page 33. There were 173,311 patients who entered a 19-day lockout from 2017 to 2022. Among these patients, there were 12 pregnancies. The pregnancy rate is 0.06 per thousand.

DR. LaCIVITA: I'm not really sure what the question is, but --

DR. LIU: This is much lower. Think about the burden we put on this and the yield. We want to identify as many pregnancies as possible given the cost, but look at the entire iPLEDGE. The iPLEDGE is -- I'm looking at slide -- it's from [indiscernible] reports. That's about 1 pregnant

per 1,000 patients. That's the entire pledge, right?

DR. LaCIVITA: We certainly appreciate your perspective, and this is a topic that we do want advice from the advisory committee. That was one of our, I think, discussion questions, or voting questions, I think. We do understand that there's burden, but we also understand that it's the last opportunity to prevent pregnancy, so I think we look forward to that discussion with the committee.

DR. LIU: My comment is, if we look at the effort we put into this and the pregnancy, we can identify from the effort we put in. So if you look at the iPLEDGE for the entire reports, we have about 1 pregnancy -- the pregnancy rate is about 1 per 1,000 women who can become pregnant. That's 1 per 1,000. That's the statistics. If we look at the yield from the lockout, we have 12 pregnancies from about 170,000 women. That yield is about 0.06 per thousand.

DR. LO RE: I think what the committee, Dr. Liu, will have to weigh is what is this

threshold that would be considered important with which to do away with such requirements. I think it's good that you pointed that out, and that will be food certainly for discussion throughout the rest of today's question period, and certainly through tomorrow.

If I could just have a follow-up, just as chair, just to follow up. From Dr. Epps' presentation, Dr. LaCivita, she mentioned that in October of 2006, there was a 23-day lockout period, but then that lockout period was reduced to 19. I just wanted to get a better sense -- it was made clear to us in Dr. Crist's presentation that the 19-day lockout captures 97 percent of pregnancies.

Could you just give us some sense of what was the rationale behind the original 23-day and what was the discussion? I think it was perhaps a joint DSaRM and DODAC meeting in 2006 that led to this change, but just to help us get some clarity, if possible.

DR. LaCIVITA: Sure. I'm going to ask Dr. Crist to help us with that question, and then

also ask Dr. Epps if she has anything to follow up with.

DR. CRIST: Thank you, Dr. LaCivita.

So the question was related to the elimination of the 23-day lockout, and moved down to what is now known as the 19-day lockout or the 19-day wait.

When iPLEDGE was first implemented 16 years ago, all patients had a 7-day window for picking up their prescription, and this resulted -- if they did not pick up or they did pick up -- in a 23-day lockout until the next prescription. This was removed for males and females not of childbearing potential, which was the terminology at the time, to reduce access barriers and reduce burden on stakeholders. The 23-lockout for females of childbearing potential was also proposed to be eliminated for all fills, with the exception of the first fill by the applicant in 2006, and this was related to burden and frustration related to treatment interruptions.

The rationale to keep this wait period for

the first fill was based on labeling, which outlines the need for two pregnancy tests at least 19 days apart before treatment has started. So this became the 19-day waiting period or the 19-day lockout. And as we've mentioned, or as I've mentioned in the presentation, this was another layer of screening to prevent people who were pregnant from starting on isotretinoin therapy. Thank you.

DR. LaCIVITA: Dr. Sun, did you have anything to add to that?

DR. SUN: Thank you. I don't have anything else to add.

DR. EPPS: Hi. Roselyn Epps, Dermatology and Dentistry. I'll just add it was the assessment or the recommendation of that advisory committee meeting that reducing that lockout or waiting period to 19 days would reduce the burden, and not necessarily increase the risk and have a problem as far as safety was concerned. That was a modification that was made to reduce the burden for patients, as well as the prescribers.

DR. LO RE: I appreciate the clarification. Thank you.

I know Dr. Hernandez-Diaz had her hand up, but it doesn't look like now.

I don't know, Sonia, if you have a follow-up question.

DR. HERNANDEZ-DIAZ: Hi. Sonia Hernandez-Diaz. I had a follow-up, a clarifying question, from the discussion before, but probably the FDA colleagues can answer.

When we were discussing patients that cannot become pregnant to reduce their burden and allowing not having the RMA, in one response it was mentioned that one of the potential risks is that then they might get the prescription from a prescriber, from a healthcare provider, that is not certified. So I wanted to get that clarification of why would that be? Why cannot we require that to prescribe you have to be certified?

Along those lines, if the recommendation is not to increased the number of days of the prescription from, say, 30 to 90, would it be

possible to have, not the prescription, but have a system for patients that cannot become pregnant trigger three RMAs from the same prescription? Still there will need to be a prescription and the information. I had another follow-up question, but maybe if we want to take this clarification first. Thank you.

DR. LO RE: Dr. Hernandez-Diaz, was that to agents, to the FDA, or to --

DR. HERNANDEZ-DIAZ: Initially it was to IPMG, but I think FDA will know also do we need to be concerned that prescribers that are not certified can be prescribing isotretinoin if we do not require the RMA for patients that cannot become pregnant.

DR. LaCIVITA: I ask the IPMG to start with that question since it was one of their proposals.

DR. LO RE: Sure.

Mr. Shamp?

MR. SHAMP: Jim Shamp from UBC. So the requirement in iPLEDGE is that any prescriber that is going to prescribe isotretinoin must be

certified in the REMS, but the concern is that a patient may be getting a prescription from a prescriber that's not aware of that. Let me give you an example that might help explain this.

Let's say we have a patient who is about 18 years old starting isotretinoin, gets their first prescription from their dermatologist at home, and then goes away to college. It's time for their next prescription, and they go to the student health center on campus and says, "Hey. Can you give me a prescription for isotretinoin?"

That doctor may not be aware that there is a REMS and it is required to be certified in order to write a prescription for isotretinoin, and may write that script. As we described before, that script can then be taken to a certified pharmacy, and because that patient is in a qualified-to-receive state, then that dispense will be authorized, and that patient will be getting drug in that situation. Thank you.

DR. HERNANDEZ-DIAZ: So it will go around the system even when that's not supposed to happen.

Since I have you, if I may, the question about would it make sense in the system to propose that the qualified prescriber for a person that cannot become pregnant can trigger three RMAs or more, they will cover three or four a prescription. So still the prescription will have to come from the prescriber, but the patient will not be in the situation of going to the pharmacy and say, "Oh, your clinician, your prescriber, forgot to do the RMA," but that way we'll reduce the burden for the prescriber, and they only have to click once but have three every 30 days trigger. Would that make sense?

MR. SHAMP: Jim Shamp from UBC. If I can clarify and maybe restate your question a different way, are you suggesting that for a patient who cannot become pregnant, that we would allow refills instead of requiring a new prescription for each fill?

DR. HERNANDEZ-DIAZ: I had that in mind, but since it was discussed that we don't want to have so many drugs around, rather than affecting the

prescription of the refill, but rather having the system triggering 3 RMAs or 4 RMAs from the clinician the first time so that the RMA is the thing that is automatically refilling, if you wish, not the prescription, but the RMA.

MR. SHAMP: Okay. Thank you. I understand your question now. So you're asking can the system then trigger, after that first confirmation, for risk management authorizations. The system only checks at the time of dispensing to ensure at that moment that all safe-use conditions have been met. So what you're suggesting is that's done possibly 4 months ahead of it, and I think just to balance the safety of this, we would need to check that each condition is met at the time of dispensing and not upfront 4 months before. Thank you.

DR. HERNANDEZ-DIAZ: If I may, can I have my second clarifying question?

DR. LO RE: Of course.

DR. HERNANDEZ-DIAZ: Thank you. The FDA probably would be in a position for this follow-up question. It is regarding actually how to reduce

the burden for patients that can become pregnant.

Regarding the pregnancy testing, based on the pandemic experience with the COVID testing and so forth, do you see, as the FDA, a way to implement the lessons learned from there to what we are discussing today? For example, that each prescription will come with a pregnancy test, with a barcode, and that the patients at home could show to an online data platform, maybe before and after, and that negative pregnancy will go straight to the system rather than having to go to the doctor, like facilitating the in-home but not completely avoiding but reducing the risk that you mentioned of falsification and so forth, by lessons learned from the COVID testing. Thank you.

DR. LaCIVITA: I'll start, and then maybe IPMG might want to add to that.

I think the lessons learned from the COVID testing is that not enough information was collected to really make that type of a determination. We do know that there were some use of home pregnancy testing. We don't really know

how much or how often that was; that wasn't collected.

So I think what you're proposing is, is there any way to kind of automate some of these actions in terms of a pregnancy test that would go directly to a pharmacy? I think that's what your question is. It's certainly an interesting thought, but that's not really something that we have discussed internally at this point in time, or if there's a capability to do that.

DR. HERNANDEZ-DIAZ: Thank you.

DR. LaCIVITA: And I didn't know whether IPMG wanted to add to that.

MR. SHAMP: Jim Shamp from UBC.

Dr. LaCivita, as you mentioned, it is an interesting idea. The issue with it, I believe, would be that in order to automate or provide an electronic interface to obtain the lab results, there are so many lab systems out there, that to be able to interface with them all would probably be not a burden that we could overcome with this system. Thank you.

DR. LO RE: Great. Thank you.

Alright. I'm going to go back. I'm going to start at the top of the order.

Dr. Green, I have your hand up.

DR. GREEN: Yes. Thank you. I had a few questions. The first is actually two parts. It involves the website. I'm not sure who best to direct that to. Two questions about this is when you enter someone's form of contraception, there are both hormonal and non-hormonal IUDs listed. I really don't see the point of that. If they have an IUD, they have an IUD; it really doesn't matter. That is a potential mismatch when it comes to contraception that comes up at times.

The other question I had, I have it up. I'm not going to share my screen, but the patient counseling, you have to check two boxes at the top. One is that, yes, you feel that the patient is capable of meeting the requirements of the system. The second -- well, the first one on the list -- is, "I have counseled this patient on the following," and the first is that they have to use

two forms of birth control. And then when you scroll down and enter their forms of birth control, you have to click a button saying I provided contraception counseling to this patient, and you have to do it every month.

We're all using EMRs. It is a lot of burden. We're all trying to reduce clicks. Basically, this is redundant. I think the part we have to enter the date should be taken out since we already entered their forms of contraception, we entered their pregnancy test, and we checked the box saying that we talked to them about this already.

Those are my two questions. I have other questions. I have two more. I don't know if you'd rather me ask them all right now or if someone wants to respond to the first; however you would like to proceed.

DR. LO RE: Why don't we do these two first just so people don't get overwhelmed. Who do you want to direct this to, the website?

DR. GREEN: Whoever is in charge of the

website.

DR. LO RE: Mr. Shamp?

MR. SHAMP: Jim Shamp from UBC. I'm going to answer your questions, but before I do, I do have an update from a question that was asked before lunch by Dr. Tollefson, if I may respond to that. The question was that we have 12 pregnancies that were reported in patients who had entered the 19-day wait. Slide up.

We have some updated information on this. Of those 12 pregnancies that were detected, three of these pregnancies were detected in the 19-day wait period; 7 pregnancies were detected after the 19-day wait period; 1 pregnancy was found to have actually occurred prior to the 19-day wait period, but the initial 7-day window was created with a negative test result entry; and then the last one is a pregnancy that was unknown due to no pregnancy test reported, and the pregnancy ended in a spontaneous abortion.

DR. TOLLEFSON: Thank you. That's helpful.

MR. SHAMP: Back to your question, I think

the first one was entry of the contraception choices online and why if you're using a hormonal contraceptive choice such as hormonal IUD, why would you need a second form. The reason --

DR. GREEN: No. Can I clarify? You have hormonal IUD and non-hormonal IUD listed. I think it should just say "IUD" because it is a potential mismatch. When the patient goes to answer their question, they can put the opposite. If you put hormonal, they put non-hormonal, and it gets blocked because it's a mismatch.

MR. SHAMP: Thank you. I understand that. I would suggest that from a pregnancy registry standpoint, that it would be important for pregnancies to understand if it was an IUD or a hormonal IUD, but that is certainly something that we can discuss with the agency and with our stakeholders.

DR. GREEN: Yes. I'd be curious to see if Dr. Sun as an OB/GYN has any comment on that because it's listed under the FDA's non-patient dependent. It's an IUD, so -- anyway, it's a

potential mismatch.

The other question was about basically being redundant on listing that we've counseled them.

MR. SHAMP: I think your suggestion was that we remove the dates on counseling.

DR. GREEN: Correct.

MR. SHAMP: That is certainly an idea that we can, again, discuss with the agency and with the stakeholders, and see if that is something that would potentially reduce burden while still maintaining the safe-use conditions and preventing exposure to fetuses. Thank you.

DR. GREEN: Great. Thank you.

I have two other questions. The first has to do with the 7-day window, and I don't know who to address this to. I'm sorry; there are a lot of people here. I don't know if anybody would be willing to consider making that a 10-day lockout window. I have two reasons; well, really one big reason.

The first is this medicine is constantly requiring a prior authorization. The prior

authorization, some insurances will tell you they have up to 7 days to get back to you, so they don't start that prior authorization until the prescription is put in. So once the prescription is put in, if they have 7 days to get back to you, that 7-day window may be up, which kicks you into the 19-day lockout period.

I have a lot of comments on that. I know it's a discussion for later, but is there a way to consider making that 7-day lockout a 10-day? Because, yes, there's us, the people prescribing it; yes, there are the patients; yes, there is the pharmacy, but I think we're leaving out a major player here, and that's the insurance company, and they have wrecked more of these prescriptions than -- I mean, this is my 18th year of doing this.

I'm a pediatric dermatologist. I prescribe a lot of this. I've probably prescribed it -- I don't even want to guess how many thousands of times at this point in my career, and I've seen it happen over and over and over again. Myorisan is no longer being manufactured, and that has created

sort of a back-jam, a backlog, so now places don't have it. They have to order it. That's a problem in and of itself. So just those 3 days I think would account for a lot of those issues with prior authorizations.

Again, I'm sorry; whoever feels best qualified to comment on that.

MR. SHAMP: This is Jim Shamp from UBC. I will start the answer, but I will ask for FDA to chime in on the specific data that they presented this morning on the patients that are able to pick up their prescription in the 7-day window. I don't recall their specific percentages.

I just also want to clarify that I think you used the word 7-day and 10-day lockout, and I just need to clarify you were talking about the 7-day --

DR. GREEN: Window.

MR. SHAMP: -- window. Thank you.

DR. GREEN: Yes, and really for the initial prescription because the prior authorization only has to come the first time you prescribe it,

generally, unless something happens where they switch insurances. But if we could make that longer, I think it would be a huge help.

MR. SHAMP: So from a program perspective, we would still have to balance the burden of this 7-day versus a 10-day window against the aspects of the safety, which is the safe-use conditions and ensuring that we are preventing fetal exposure to isotretinoin. But I would again ask if FDA could provide their statistics or the percentage of those patients that were able to get a prescription filled in that 7-day window. Thank you.

DR. LaCIVITA: This is Cynthia LaCivita from the FDA. I'm going to ask Dr. Crist to answer that question, but I just want to make sure before she answers the question, you're speaking only of female patients who can become pregnant. They're the ones that have the 7-day window, and your question is to extend that time period for the first prescription window to 10 days. So I just wanted to make sure that I understood the question.

DR. GREEN: Right, yes.

DR. LaCIVITA: Dr. Crist can follow up with the statistics that we had on our side. Thank you.

DR. CRIST: Thank you. Lindsey Crist from the FDA. Sure. The statistics that we summarized from supplemental -- I'm sorry. Can you guys hear me now? I apologize

DR. GREEN: Yes.

DR. LaCIVITA: We can.

DR. CRIST: The data that we presented was supplemental data from the IPMG that stated that 80-to-85 percent of patients who can become pregnant are able to pick up the prescription, the first prescription, within the 7-day window.

DR. GREEN: Is that people who can -- I guess it would be people --

DR. CRIST: Yes, patients who can.

DR. GREEN: Okay, because it just seems to happen a lot with the prior authorizations, and that 15 percent then kicks into that 19-day window, which becomes a problem in and of itself.

Anyway, that's my suggestion. I guess it's something we can talk about at a later time since

we're really just doing questions here. I do have one more question if you guys don't mind.

When it comes to the home pregnancy test, my question for you guys is what data are you looking for? Because if we say home pregnancy tests are not allowed to count towards your, you have this negative pregnancy test; we can put it in the system, you will effectively kill the ability for anyone, any female of reproductive potential who could get pregnant, to use telemedicine as an option. It will derail the entire thing.

We've been doing this since the beginning, and we've probably done a few thousand patients this way. We have no reported pregnancies using home pregnancy tests. Would you be willing, for the next year, to say, "You know what? We're going to keep track of pregnancies as we always have, but we're going to parse out how many people were reported pregnant from the CLIA pregnancy lab." How many people were reported pregnant using this as a home method -- using a home pregnancy test? Excuse me.

MR. SHAMP: Jim Shamp from UBC. That is exactly what type of data we would need, is of the pregnancy tests that are entered, how many of them are from a home pregnancy test or how many are from a CLIA-certified laboratory conducted test, and then we would need to have sufficient data to be able to measure the pregnancy rate and see if there is any type of a variance in those two different types of tests.

DR. GREEN: Understood. I mean, the pregnancy rates haven't gone up during the pandemic -- I know that's a lot of factors that go into that -- but home pregnancy use tests have gone way up.

Alright. Those are all my questions --

DR. LO RE: Yes, this sounds like this would be an area for more research in the future.

DR. GREEN: Yes. That's something we can certainly look into. But I guess as someone who uses a lot of telemedicine, and I think all of us are in this boat now clinically, if you say, "Hey, we cannot use home pregnancy tests," you're

basically telling every female who's registered --

DR. LO RE: Dr. Green, let's just keep this for clarifying questions. We'll have time for discussion and more opinions, though, tomorrow, if that's ok.

DR. GREEN: Understood. Understood. Out.

DR. LO RE: Dr. Schreiber, you're up next.

Oh, wait. Actually, before Dr. Schreiber, I was just notified by our designated federal officer that Dr. LaCivita wanted to make one clarifying point. I'm sorry.

DR. LaCIVITA: Yes. I'm sorry. I think Dr. Wenjie Sun, she wanted to make a clarifying point regarding the 97 percent. I think that's a question you had asked.

DR. SUN I think I heard it earlier that you stated that 95 percent of pregnancies can be detected through the 19-day lockout. I just want to point out that it is true that a pregnancy conceived prior to the lockout, the detection rate is approximately 97 percent, but for those pregnancies that conceived during the lockout, the

percentage is little bit lower than that. For those with regular cycles, we are estimating about 40-to-66 percent. Thank you. That's just a point of clarification.

DR. LO RE: Thanks, Dr. Sun.

Dr. Schreiber, I have you up next.

DR. SCHREIBER: Hi. Thank you.

My clarifying question is around abstinence and how it's classified in the REMS, and how it relates to the request posed to this group to evaluate the need to continue or modify the pregnancy registry because a value stated of the registry is that it allows the conduct of root cause analysis for the pregnancies, and I wonder if the registry is in fact used that way.

For example, when we look at what factors are most associated with a pregnancy while on therapy, the stated lifestyle choice, abstinence, is one factor associated with a pregnancy while on therapy. And I note that abstinence is classified here as a lifestyle choice and not as a contraceptive method, but it could be classified as

a contraceptive method, which is, by the way, the REMS functions that there would be a requirement for a second method, a backup method, because all the other contraceptive methods require two.

So I wonder if there's ever been a consideration for requiring two methods for those who state that abstinence is their method, and I also am asking if patients who state that they are abstinent are also undergoing contraceptive counseling at the outset of some sort; so that, for example, if a failure of abstinence is identified, those individuals might have resources and ready for emergency contraception, or if they are anticipating a possible failure, how they are connected with contraceptive care. Thank you.

DR. LO RE: Dr. Schreiber, do you want to direct this to the agency or to --

DR. SCHREIBER: I wish I knew to whom I should best direct that question. I don't.

DR. LO RE: Okay. I'm going to ask maybe Dr. -- Dr. LaCivita, you popped up. Did you want to --

DR. LaCIVITA: I was just getting ready just in case. Go ahead.

DR. LO RE: I was going to ask Mr. Shamp first.

DR. LaCIVITA: That's fine.

DR. LO RE: Dr. Ephross had talked a lot about the registry.

MR. SHAMP: Jim Shamp from UBC. Your first question about have we considered allowing abstinence and a form of contraception, prior to a change in the system of few years back, we actually allowed the entry of abstinence and a form of birth control, but that was removed primarily because the concept of abstinence means you really should not need another form, and if you're considering not being abstinent, then you need to be having that discussion with your prescriber and moving on to a specific combination of birth control choices.

Your second question I believe had to do with for patients that choose abstinence, are they still provided with the counseling? That is the requirement of the REMS, is that the patient is

counseled by their prescriber on contraception, and if that prescriber does not feel comfortable or knowledgeable enough to have those discussions, that they are referred to a contraception counseling expert. So depending upon their choices, they should also provide the contraception counseling per the requirements of the REMS.

I apologize. If you could just restate your third question; at this point, I have forgotten it.

DR. SCHREIBER: Thank you. It was only related to just trying to tie a bow around the whole process here as it relates to the need for the pregnancy registry or any modifications to it because, to me, as we look at the pregnancy outcome data, those who state abstinence is there method or their lifestyle choice have one of the highest risks of becoming pregnant while on therapy.

So if the goal of the REMS is to prevent pregnancies while on therapy, then perhaps -- I guess my question is, why did that change happen that you just alluded to; that people who choose abstinence, which is a less effective method than,

for example, a long-acting reversible contraceptive method, are not required to use two methods, and the data support that perhaps they should be.

MR. SHAMP: Jim Shamp from UBC. I'll ask Dr. Ephross to respond to the question, but before she does, I would just like to state that isotretinoin is approved for patients 12 years and older, so I think from a perspective of those younger patients, we do need to take into consideration that lifestyle choice, specifically based on their age.

Dr. Ephross?

DR. EPHROSS: Sara Ephross, Syneos Health. Slide up, please.

Dr. Schreiber, I think this is the slide that you're referring to; is that correct, the unsuccessful at abstinence?

DR. SCHREIBER: That's exactly right, yes.

DR. EPHROSS: This is showing it for the prescriber reported reason for pregnancies. These are the data that we're talking about, and I think that the simple answer is that the way abstinence

is defined in this program is that there is no way that you could need a second form of birth control. In other words, the way that it is defined, nothing is happening that would require you to be using birth control. Thank you.

DR. LO RE: Any other questions, Dr. Schreiber?

DR. SCHREIBER: No. Thank you.

DR. LO RE: Dr. Katz, I have you up.

DR. KATZ: Thank you. It's Ken Katz. The first question relates to the 19-day lockout period and the 12 pregnancies that were detected in people who were in that lockout period.

Do we have information on the primary and secondary forms of birth control that those people were on, and specifically, were there any pregnancies in people who were on long-acting contraceptives who became pregnant?

MR. SHAMP: Jim Shamp from UBC. I don't believe we have the specifics on those 12 patients that became pregnant that were in a 19-day wait, but what we do have is the most common

contraception methods and the pregnancies. Slide up.

So what you can see here is years 14, 15, and 16, that abstinence was the most common choice of the birth control and with the birth control pills and male latex condoms as the second most popular choice. But you will see in year 16 -- I'm sorry. I misspoke. Hold on. I'm trying to understand all the data here. Yes, for patients who were not pregnant, abstinence was the most common. For patients who became pregnant, the birth control pills and male latex condoms was the most common choices.

DR. KATZ: Right. I see. I think it would be interesting if we're able to get the data on those 12 because it might be helpful to stratify the risk. I know the comment was made earlier that the system was kept simple so there wouldn't be confusion, but we doctors can keep a lot of balls in the air at the same time. So if the risk is extremely low, or zero, we think in patients who are on long-acting contraceptive, then maybe for

those people, we could get rid of that 19-day lockout.

My second question is about sharing of medicines. Do we know in those people who shared medicines, whether that was because they didn't know they were supposed to not share it or they knew and they just decided to share it anyway?

MR. SHAMP: Jim Shamp from UBC. I don't think we collected that data for the patients that had reported they shared their medication. As we said before, we do know it was 24 cases through the life of iPLEDGE, and more recently I believe it was 4 cases where patients have shared drug.

DR. KATZ: Right. I guess it speaks to the importance of counseling. We could counsel every day, but if people are going to share it anyway, that's not going to do anybody any good in terms of thinking about burdens. Okay. Thank you.

MR. SHAMP: And if I could just add, from your previous question about the contraception choices for these 12 patients, that is something that we can try to get and provide back to you

either later today or sometime tomorrow.

DR. KATZ: Thank you. That's it. Thank you.

DR. LO RE: Ms. Robotti, I have you up next.

MS. ROBOTTI: Hi. Suzanne Robotti, DSaRM. I have a couple of questions. One's really simple I think. Do we have a dropout rate on those patients that started on treatment but dropped out before the end of the 4 or 6 months of the typical use? And if we do, do we know why they dropped out? And I don't know who to ask that.

DR. LO RE: I think Mr. Shamp might be the best.

MR. SHAMP: Jim Shamp from UBC. We do have some data on that. I'm looking for the data on lost-to-follow-up patients. We do have data for patients who became lost to follow-up during their treatment and recognized by the system from a lack of activity in the system, based on the prescribers not confirming them, and they are not completing their required activities in the system, nor are we seen authorizations for dispensing.

MS. ROBOTTI: What percentage of people who start treatment do seem to drop out, or as you like to say, lost?

MR. SHAMP: I apologize. I'm waiting for the data to come up to be able to speak to it directly.

MS. ROBOTTI: Of course the reason I'm asking is simply if the dropout rate is relatively low, that would indicate that patients are putting up with the inconveniences and finding ways around it. If the dropout rate is high, again, it depends on why it would be high, but it would be another indicator.

MR. SHAMP: Yes. Slide up.

As you can see, there are two different types of lost to follow-up that we're looking at here. One is patients who were registered and then went inactive as I described, and this one is where patients had completed their course of treatment, but we were awaiting the entry of the pregnancy tests at completion of therapy, and then the second test at 30 days after completion of therapy.

So I think your question really applies to this first row, and as you can see, it's been fairly consistent across years 14, 15, and 16, and somewhere between 14 and a half and 16.6 percent of those patients.

MS. ROBOTTI: I mean, the side effects are fairly significant separate and aside from the effort of getting the drug. Do you have any feel for or any data on the dropouts? They do not want to tolerate the drug any longer, or they could not comply, or they got pregnant and didn't report that they were pregnant?

MR. SHAMP: We don't have data on these patients because they disappeared from the system and they did not interact with it. In the case where the prescriber does discontinue the patient, in that case we do collect data, but these are patients that the prescriber did not discontinue them, they did not come back, or there was a lack of interaction, which caused them to go inactive. Thank you.

MS. ROBOTTI: If you're on

isotretinoin -- the pronunciation, I apologize -- if you're on the drug, what happens if a patient takes a morning-after pill? Is there any concern about emergency contraceptive use like that?

MR. SHAMP: Jim Shamp from UBC. If I could just clarify your question, you mean from a safety aspect or what perspective?

MS. ROBOTTI: I mean from a safety aspect. If somebody feels that their birth control failed, their abstinence vow failed them, and they participate in sex and then go use a morning-after pill, that quite possibly would not ever be reported to the doctor. So I'm simply wondering is there a health effect to that, a visit? Have you looked at the interaction of the two drugs?

MR. SHAMP: Jim Shamp from UBC. I'll ask Dr. Weiss to respond to the question.

Dr. Weiss?

DR. WEISS: Hi. It's Dr. Weiss, Herman Weiss. I'm an external GYN consultant as a paid consultant to the sponsors, but I have no financial

interest in the outcome of this meeting.

The concept of the morning-after pill would be -- I mean, I don't know how the sponsors would appear, but it would be a failed abstinence --

MS. ROBOTTI: As an example.

DR. WEISS: Sure. As an example, it would be a failed abstinence, and they would use an additional form of birth control to prevent that pregnancy. I assume that they would have to be entered into a failed contraceptive and then have the adequate follow-up.

I'm not sure. If you're getting at that the emergency contraceptive isn't well represented as a form of birth control, that could be obviously added in as a potential discussion point. But as far as a potential path, I think you'd have to treat this as a failed contraceptive, and then obviously treat this pregnancy as a potential pregnancy but potentially adequately treat it with emergency contraceptive.

If I'm understanding your question, I think the goal is that these patients understand they

need contraception. They know that they promised to have abstinence, and they didn't abide by their abstinence or whatnot, so they adequately treated themselves for that, so that obviously would need to be individualized. I'm not sure the program really stands to have that individualization aspect. I hope that answers your question.

MS. ROBOTTI: It does. I just can't help but wonder about things like somebody who realizes mid-month that they are pregnant, and then uses the two-step pregnancy pill, and therefore isn't pregnant, and continues through continuous treatment, probably I guess all fine. Sorry, just wandering thoughts on what can go wrong here.

DR. WEISS: Yes. I think we're just mixing up two things. There's the morning after pill, which is --

MS. ROBOTTI: No, no. I know. I'm going on to a different example.

DR. WEISS: Yes.

MS. ROBOTTI: Yes, as an example. There are just lots of things that can go wrong here.

Someone can end up with ending a pregnancy without ever telling their dermatologist, and, I mean, I don't know that that matters. I guess I'm asking does that matter.

DR. WEISS: Well, I'm not sure. If they keep doing the testing on a month-to-month basis, when do they have the opportunity to enter properly? According to your first scenario, they took the morning-after pill, so they never got pregnant with the morning-after pill. Going to your second scenario, they were using the Mifeprex or the antiprogesterone, and that would be the [indiscernible].

MS. ROBOTTI: Exactly.

DR. WEISS: So that's entirely different. They're definitely going to have that 30- window.

MS. ROBOTTI: Right, if they couldn't, then the 30-day window.

DR. WEISS: They can have that. So yea, I don't think that would be the issue.

MS. ROBOTTI: Okay. Just a last thing. There are home COVID tests for people when they're

required for traveling internationally. You could get a sealed box, and use a code, and register it, and get a COVID test that was accepted by international borders.

Is there a way for home pregnancy tests to create such a difficult structure but it's easier than going to the office? I say this because I personally think that home pregnancy tests, as they stand now, are way too easy to take, and in the place where the country is now with abortions, elective abortions are becoming more and more difficult to get. It's more and more important that pregnancies don't happen.

Has anyone looked into that, comparing the international COVID tests to home pregnancy tests with their systems?

MR. SHAMP: Jim Shamp from UBC. We have not looked into that suggestion, but as you heard Dr. Wedin present earlier, there are some concerns and risks associated with the home pregnancy tests, and the IPMG sponsors do align with FDA's recommendation to allow the pregnancy tests being

performed in the prescriber's office using a CLIA-waived test. Thank you.

MS. ROBOTTI: Okay. Thank you.

DR. LO RE: I want to just circle back. I saw Dr. LaCivita and Dr. Sun had their hands raised. I don't know if they wanted to respond to one of Ms. Robotti's questions. I know that Phil Bautista had said that the agency wanted to make a comment about a question that Dr. Katz had raised about the 12 pregnancies during the 19-day lockout.

DR. LaCIVITA: Yes. I'll call on Dr. Sun. She has some information on the 12 pregnancies during the lockout. Thank you.

DR. SUN: Yes. Thank you. This is Wenjie Sun from FDA. We're trying to answer Dr. Katz's earlier question regarding what contraception was used in the 12 pregnancies that was detected during the 19-day lock out in the last few years. For these pregnancies, six of those patients were using birth control pills and male condoms for contraception. One was using abstinence and the rest have unknown methods of contraception. Thank

you.

DR. LO RE: Dr. Katz, any follow-up from your side? Just circling back.

DR. KATZ: I wish we had full data on the other six, but I appreciate that information. Thank you.

DR. LO RE: Great.

Dr. LaCivita, was that the key comment or anything else?

DR. LaCIVITA: Nothing else. Thank you.

DR. LO RE: Okay. I am going to return to the top of the queue.

Dr. Delost?

DR. DELOST: Thank you. Kort Delost, community pharmacist. I first wanted to verify this to IPMG. After listening to Dr. Hernandez-Diaz's question, I want to get a point of clarification.

The RMA that's created, isn't that linked to prescriber in themselves?

MR. SHAMP: Jim Shamp from UBC. The RMA does confirm that the safe-use conditions at that

moment have been satisfied, and with the current system requiring the confirmation monthly for both patients, the patients who can become pregnant and patients who cannot become pregnant, we do have the linkage to the prescriber, and we can confirm the prescriber was certified at the time of that confirmation. For patients who cannot become pregnant, if we remove that linkage, we no longer know for certain who that prescriber is, and we cannot determine if they are certified.

DR. DELOST: Could you still keep that RMA, and if you didn't have it, it would just reject at the pharmacy, and we'd know right away it was not a correct description from another doctor?

MR. SHAMP: Jim Shamp from UBC. The RMA does not get generated until the pharmacy tries to fill that prescription, so it's not to be created at any point in time except when the pharmacy obtains the RMA. I think what you're suggesting is could then the pharmacy confirm that the prescriber on the script is certified, and we don't have a specific solution in mind at this point. We have

been discussing a solution to this, but it's important to understand that any solution at this point would put additional burden on the pharmacy, which we're trying to reduce burden. We're trying to reduce it from the prescriber, and it would just simply shift it to the pharmacy. Thank you.

DR. DELOST: Just follow-up. If they had a way of making it like an exempted claim for a person that cannot get pregnant, we could still use the RMA system to fill it, and it could indicate maybe at the time we feel that, that this was an exempt prescription that was prescribed by the doctor, and it's a valid prescription, still, with the RMA.

MR. SHAMP: Jim Shamp from UBC. I apologize. I don't understand. If you could clarify what you mean by an exempt prescription.

DR. DELOST: Well, say it would be exempt from the -- well, we won't use the word "exempt." It would just be when you went to fill, it would already be pre-approved by the doctor. It's connected up to that doctor. So if we could

connect that doctor to when we generate the RMA, and if there was another doctor trying to prescribe it, there wouldn't be a linkage to be able to do that prescription, would there?

MR. SHAMP: Jim Shamp from UBC. I think the only way that we could detect whether there is a correct linkage or incorrect linkage with the non-certified prescriber is to require entry of some data at the pharmacy at the time they're trying to obtain the RMA, and that is the very specific point of increasing burden to the pharmacy as we're trying to reduce it from the prescriber.

DR. DELOST: I want to say this program you have in place should be able to -- it wouldn't require any more burden just entering the prescription like any other prescription that came in for that. I don't know where the problem would be.

MR. SHAMP: Well, we appreciate that thinking, and we can certainly discuss this idea with FDA and other stakeholders. Thank you.

DR. DELOST: Thank you.

DR. LO RE: Dr. Salvas, do you have a question?

DR. SALVAS: I do. Thank you. Brian Salvas, CVS Health. A question to both the FDA and and the IPMG. I'm curious what opportunities exist for testing and learning and pilot testing as it relates to different program designs to be able to collect the data that's lacking around blocked prescriptions, allowed prescriptions, the qualitative elements around both provider, and patient, and caregiver experience.

Is this something that's possible within the current scope of the iPLEDGE program?

MR. SHAMP: Jim Shamp from UBC. We appreciate the question, specifically the thinking around this pilot testing. That is certainly something we'd be happy to discuss with the agency and with our stakeholders. I certainly open the floor to the agency to see if they have any additional comments. Thank you.

DR. LO RE: Dr. LaCivita?

DR. LaCIVITA: This is Cynthia LaCivita from

the FDA. I think we're always trying to look for ways to reduce burden, and this is something that we can certainly continue our discussions with the IPMG. Thank you.

DR. SALVAS: Thank you.

DR. LO RE: Dr. Cowen?

DR. COWEN: Thanks. So my questions, if we can pull up slide CM-12 from the IPMG presentation, the 120-day confirmation interval, I'd like to revisit the rationale for how the 120 days was chosen.

Looking through the recommendations, one of the few areas where I think there will actually be a prescriber burden reduction is individuals who cannot become pregnant and fewer touches the prescriber needs to have with iPLEDGE. The rationale for 120 days I believe was this was approximately a month before the mean duration treatment. I would consider the median duration of treatment as being much more important. You can see a large number of patients drop out in their first month either due to logistics or side

effects, and the vast majority of patients are treated for 5, 6, 7 months.

So I'd just like to hear the rationale again for having the prescriber go into the system once more, a month or 2 months, before completion of therapy to testify that this counseling is occurring on a monthly basis.

MR. SHAMP: Jim Shamp from UBC. I will ask Dr. Wedin to respond to the question.

Dr. Wedin?

DR. WEDIN: Greg Wedin, Upsher-Smith Laboratories. We will investigate to find out what the median is. It seems to me the median and mean in this data set are very close, but we'll try to get that number for you.

You're correct in your assessment that what this accomplishes is that just prior to the prescription, the beginning, the fifth month of therapy, this 120-day confirmation interval would require documentation that the prescriber has evaluated that the patient has determined they need continued therapy, and that they have counseled the

patient on safe-use conditions, and that counseling takes place at a point in time where most everybody who gets that counseling at 120 days will likely finish therapy before they would require, yet, additional counseling prior to month 9.

So that is our rationale, is that we feel that that patients who require therapy beyond that mean or median duration of therapy, that they do receive that counseling before they finish therapy. Thank you.

DR. COWEN: Just to follow up on that, so the goal is that there is two touches that occur. Even if the person is going to be going off therapy, we always want an endpoint documentation made as well?

MR. SHAMP: Jim Shamp from UBC. Dr. Wedin will respond to the question.

Dr. Wedin?

DR. WEDIN: Greg Wedin, Upsher-Smith Laboratories. That is correct. We would like for those patients who are going to continue beyond the mean or median course of therapy, that there is an

additional touchpoint where prescribers interact with the patient; reinforce safe-use conditions; not to share any leftover medication that they might have; not to donate blood; and how to dispose of drug properly. That last one is not a requirement of the REMS, but I think it would be important in that situation.

DR. COWEN: Okay. It sounds like you're saying continuing beyond a normal course of treatment, you'd want a second round of counseling versus just having a second round at some point along the way. So if patient had a normal 6-month course, they would or would not need to get this?

DR. WEDIN: If a patient had a 6-month course of therapy, they would receive the initial counseling with the initial prescription, and then one additional counseling would need to be documented at 120 days prior to that prescription during the fifth month.

DR. COWEN: Thank you.

DR. WEDIN: Thanks.

DR. LO RE: Can I just have a follow-up,

Mr. Wedin?

So patients who cannot become pregnant are still coming in on 30-day intervals to their provider for their prescription fills; correct? I thought that you had said earlier that those patients are still being counseled on a month-by-month basis, but that the counseling in this kind of a scenario, with a 120-day confirmation, they wouldn't necessarily be documented within the system; is that correct?

DR. WEDIN: Yes, that's correct. Currently, a monthly counseling of patients who cannot become pregnant is required, but the documentation of that counseling is required currently with each prescription. This proposed 120-day interval would not require documentation in the system that that counseling took place unless the patient did receive a prescription after that 120-day interval. Then they would need to be counseled once again.

DR. LO RE: Okay. And just two follow-up questions to Dr. Cowen's, the reason for this is really because of concerns about blood transfusion

and dispersal of drug; is that correct? Is that the main concern for why there is a sentiment that we want an additional touchpoint?

DR. WEDIN: Was that question for me?

DR. LO RE: Yes.

DR. WEDIN: Yes. The documentation at the 120-day interval would be to confirm that that counseling did take place, and that the prescriber has determined that additional therapy is needed and, again, we then have documentation that that did take place.

DR. LO RE: Okay. And my second question is you mentioned, and Dr. Cowen brought this up, that the rationale for this 120 days was that it's just near the mean of the duration of therapy, But I wanted to just get a sense. Did you consider a 90-day or a 60-day; and if so, what were the factors that went into your thinking to select 120 versus an earlier period?

DR. WEDIN: The rationale for the 120-day, the conversation about that began with the labeling, where it's documented that the typical

course of therapy is 4-to-5 months. So as we looked at that, looking to determine should additional counseling take place, that seemed like a logical point in time for that counseling to occur.

So that's how the conversation started, and as we did evaluate durations further out from 120 days, since that has been the request for quite a long time, is to extend it out to potentially a year, our concerns with that is that introduces other risks related to sharing drug as one of the primary concerns.

DR. LO RE: And then last follow-up question, do either you, or Dr. LaCivita, or anybody at the agency have any sense, among patients who cannot become pregnant, how often is there blood donation or dispersal of isotretinoin inappropriately? Do we have any data on that? Because it seems like that's really what's driving the desire to have another touchdown with counseling.

DR. WEDIN: Yes. We did present data

earlier on the numbers of incidents we became aware of, of sharing drug. There were 24 instances detected over the course of the problem, and during the years 12 through 16, there were four other documented cases of sharing drug. And again, those are only the situations that have come to us as a result of spontaneous reports. We don't collect any data that would signal that so that we could actively collect it.

I do have follow-up information on the question from Dr. Cowen. The median duration of therapy is 6 months.

DR. LO RE: Great.

DR. COWEN: Thank you.

Dr. LaCivita, did you want to make any comment?

DR. LaCIVITA: You had just asked if we had any data. This is Cynthia LaCivita from the FDA. We do not have any data. The data that we have would come from the IPMG. Thank you.

DR. LO RE: Thanks.

Dr. Ludwinski?

MS. LUDWINSKI: Thank you. Donna Ludwinski, patient representative. I had a question about slide 34 from Dr. Crist's presentation, and it has to do with the post-treatment pregnancy test requirement, because the review team recommends keeping that. But what strikes me about those numbers is 5 percent completed both and 14 percent completed one or the other, and yet almost 10 percent of the reported pregnancies occurred within the 30 days of stopping.

So my question is, does that imply that the rates of pregnancy in that 30-day window afterwards could be really much, much higher than what's getting reported? I know it was mentioned earlier that it's awful hard to incentivize anyone to come back, but it makes me wonder about that 14 percent that completed either the first or the second. If they only completed the first, then that would miss that whole 30-day window, but if they completed the second, that would cover the first.

So I'm curious. If most of that 14 percent did the first one, and if there is more of an

incentive to come back for the first one versus the second one -- sorry, I didn't make that crystal clear, but it's mostly to do with what potentially are the true rates in this group and how that can be determined.

DR. CRIST: This is Lindsey Crist from the FDA. To your first question, which I believe was could it imply that the rates are higher in this post-treatment period, I want to just note that there is likely underreporting in this period since very few patients complete these tests.

Your second question, I believe, was related to specifics on the distribution of how many completed the second test compared to the first test. I don't have that data at the moment. I will defer to my colleague, Dr. Kiruthi, although we may need to defer to the IPMG for those specifics. Thank you.

MS. LUDWINSKI: Thank you. That's all.

DR. LO RE: Dr. Kiruthi, did you want to make a comment. I see you came on camera.

DR. KIRUTHI: Sure. Thank you. My name is

Dr. Wambui Kiruthi. For the record, I'm with the Division of Mitigation Assessment and Medication Errors Surveillance. I am one of the REMS assessment analysts. I believe it was 5.36 percent that had completed both tests.

DR. LO RE: Thank you very much, Dr. Kiruthi.

DR. KIRUTHI: Yes.

DR. LO RE: Mr. Shamp, did you want to make a comment?

MR. SHAMP: Yes. Jim Shamp from UBC. We actually have the same data as was just commented. For year 15, it was 5.23; for year 16, it was 5.36. And it was also 5.36 for year 4 that completed both tests. Thank you.

DR. LO RE: Thank you.

Dr. Huybrechts?

DR. HUYBRECHTS: Krista Huybrechts. I just had a follow-up question related to the additional data that were shared, that for the 12 pregnancies that occurred during that 19-day lockout window that the method of contraception was not known, I

was just trying to understand the mechanism behind it.

My understanding is that those patients are patients that had enrolled in the iPLEDGE system at the start and then had their two pregnancy tests, and because they were enrolled, they had to certify what the method of contraception was going to be; had their two pregnancy tests, and then missed that 7-day window, and therefore was kicked to the 19-day lockout window.

I was just wondering, given that they all had to certify in the iPLEDGE system what method of contraception they were going to use, what is the reason why we don't know the method of contraception? And the reason I'm asking is if it's documented in the system and we know they got pregnant, could that be an opportunity to flag those patients that might go on to become non-compliant with their contraception?

As I was thinking about it later, I thought maybe you don't know because pregnancies are reported outside of the iPLEDGE system, but that

was my question. Are the pregnancies that are occurring documented in the iPLEDGE system, and can we then use it to help identify at-risk patients that then can be targeted?

MR. SHAMP: Jim Shamp from UBC. I believe we do know the contraception choices as entered by these patients into the iPLEDGE REMS system. We don't have that at hand, but we will look to see if we can get that for you and provide that either later today or tomorrow.

I think there may have been a second point to your question, but I forget what that was.

DR. HUYBRECHTS: No, it was more the rationale behind my question. If we know and can identify those patients that are at risk to become pregnant during that 19-day lockout window, can that help us to maybe target at-risk patients early on, rather than having to impose a 19-day lockout window for everyone. If we knew who those patients were, then maybe there could be a more targeted intervention.

MR. SHAMP: Jim Shamp from UBC. That is one

of the reasons we try to collect the root cause analysis of the pregnancies, so that we can determine specific at-risk patients and perhaps make a modification to the system. Thank you.

DR. HUYBRECHTS: Thank you.

DR. LO RE: Great.

Are there any further clarifying questions?

Dr. Dublin?

DR. DUBLIN: Thank you. Dr. Dublin, Kaiser Permanente. I've just been thinking about the birth controls being the number one method as chosen by the women who then have pregnancies. Incredibly much lower, obviously, were the pregnancies of the women using LARC, like IUDs. I understand the desire for simplicity to treat all women the same, but as currently structured, women who have a much lower failure rate, the women with IUDs, are going through the same burdensome process, and the same monthly logging in and confirming their birth controls.

It just seems like there are some benefits to considering treating women differently who have

chosen a much more effective, like, literally, like a 10 times lower failure rate. And potentially, if you made the system somewhat less burdensome for women who choose that, it could actually incentivize women to choose these more effective contraceptives.

To me, I feel like we have two questions. I think we all understand the program is effective. We're all concerned about burden. But if you think about what are the reasons for the failures that we do have, I think user difficulty in following through with some of the methods of contraception like birth control pills, which especially as a mom of a teenager, having to take a pill every day at the same time, this is really hard on younger people to adhere with.

So I feel like we're missing kind of an opportunity to say how could this system maybe be designed in a way that makes it beneficial for patients and providers when people choose more effective forms of contraception. I wonder if that has been the subject of discussion at all with IPMG

or FDA.

MR. SHAMP: Jim Shamp from UBC. It's important to understand that all birth control can fail, and that we are aware of pregnancies that have occurred in patients selecting LARCs as their contraceptive choice, and I will ask Dr. Weiss to respond to the meaning of your question.

Dr. Weiss?

DR. WEISS: Yes. I think it's a general statement. It's Dr. Herman Weiss, external GYN consultant. It's a general statement about making sure that we're affording these patients all the choices. I personally know that perhaps a young child who has to be on the birth control pill may be not the best candidate for an IUD for obvious reasons. Perhaps a subdermal contraceptive, it has its own list of side effects. And while you may be incentivizing her to take a drug that may not be appropriate for her, you're trading one set of safety issues for other safety issues.

For example, again, this has been my experience, and I'm sure there are a lot of other

gynecologists on the call who have different experience and different expertise. In regards to the side effect profile for the subdermals in the the clinical trials, 1 percent of the patients enrolled had to have the subdermal implants removed because of acne, so 1 out of 100 would have to be removed because of acne. So that's 1 out of 100 that would have to be removed because of acne, and there are others that didn't have to be removed, that stayed in the trial but still had the acne.

I think what we're getting is, yes, we do need to communicate and try to individualize to the best of our ability, but I don't know if incentivizing is really the right tool. Again, my experience with IUDs, although they are much higher in a perfect world and a perfect placement, they do get expelled as well. Every category has different risks, and adding another layer of nuanced decision making I don't think decreases the burden of this program. It could very well increase the burden of the program when you have to figure out which contraception this person has.

Hopefully this will answer your question, but I do think that this contraceptive counseling, if done properly, does give them all the options. I just don't know if we're going to incentivize that population if that's the right thing to do.

MR. SHAMP: And if I can just add on to what Dr. Weiss was saying at the end, the complexity in this system of having different rules for different birth control choices could certainly add to the burden of the prescriber in determining the steps and when those steps should occur for the patient in the iPLEDGE system. And as with all modifications, we would certainly have to balance the burden of the changes against the safety aspect of preventing fetal exposure to isotretinoin. Thank you.

DR. DUBLIN: I appreciate the perspectives being raised, but I guess I would say, speaking as an epidemiologist, I don't find it useful to say things like all birth control can fail; therefore that's a justification for not treating IUDs differently. I mean, I think that we look at

rates. Everyone's been asking over and over again what birth control was somebody on when they got pregnant, so I think that's a little bit of a specious argument.

I also kind of want to disagree with the idea that IUDs couldn't be an appropriate choice for younger women. I mean, we're not talking about young children, but I think that we now know that LARCs are actually really safe and effective for women of different ages, and all of those women, they are appropriate. If there's a concern about that, I would ask our pediatric and adolescent gynecologists to speak to that.

I think we're missing opportunities here, and if we really are committed to trying to prevent pregnancies, we need to recognize that oral contraceptives in routine everyday use really are markedly less effective than the other choices we have, and right now we're kind of acting as if they're all equal. So thanks for the chance to share that perspective.

MR. SHAMP: Jim Shamp from UBC. If I could

have the slide up?

I just want to share data that we have on the pregnancies that occurred and the birth control choices that were in use by that patient at the time. As you can see from this slide, we do have pregnancies that have occurred in patients using these LARCs, specifically the hormonal IUD, hormonal implants, and the non-hormonal IUD. So while the pregnancy rate is lower than the overall rate, the pregnancies are still occurring in these patients. Thank you.

DR. LO RE: I just wanted to know if the agency had any comments to Dr. Dublin's question. I would point out that figure 2 on page 30 of the briefing document does highlight the differences in number of pregnancies with the different forms of contraception.

Was there any consideration to treating women differently?

DR. LaCIVITA: You mean treating differently depending on --

(Crosstalk.)

DR. LO RE: Yes, based on --

DR. LaCIVITA: This is Cynthia LaCivita from the FDA. Treating women differently with respect to which contraceptive method they use?

DR. LO RE: Yes.

DR. LaCIVITA: We are discussing that internally, but we haven't made a determination at this point in time.

DR. LO RE: Okay.

Any other question, Dr. Dublin?

DR. DUBLIN: No. Thank you. That's all for me.

DR. LO RE: Okay.

Dr. Liu?

DR. LIU: Hi. Tao Liu. I have a question about patients' comprehension and evaluation on the risk of birth defects. I know that it was shown that for patients who can become pregnant, more than 95 percent passed the test on the first try. I wonder if there is a similar test for patients who cannot become pregnant, and if there's a test, what's the passing rate?

MR. SHAMP: Jim Shamp from UBC. The questions that are asked each month to the patients who can become pregnant are specific to their contraception choices and the efforts that they need to undertake to prevent pregnancy. There are no questions that are asked to these patients that cannot become pregnant.

From my presentation earlier today, I showed that the only time these patients interface with the system is at time of enrollment, and then each of the monthly confirmation periods after that, there is no need for any patient interaction with the system. Thank you.

DR. LO RE: Great. Thank you.

Any other clarifying questions? Dr. Chambers?

DR. CHAMBERS: Hi. David Chambers from the National Cancer Institute. I believe this is a question for Dr. Crist. I noticed, on I think it was slide 33, the 15-to-20 percent of patients who can become pregnant who missed the first window. Just as an idea that there might be opportunities

to try and have fewer folks end up in that 19-day lockout, I was curious if you have information about what the main reasons why people are missing that initial window for that prescription. Thank you.

DR. CRIST: Thank you. Lindsey Crist from the FDA. We do not have specific reasons for why patients are missing that window. I can open it up to see if the IPMG has additional data to share on that. Thank you.

MR. SHAMP: Jim Shamp from UBC. The system does not collect a reason for missed windows, so we do not have that data at this time. Thank you.

DR. CHAMBERS: Okay. Yes, thanks for that. It sounds like it might be a good opportunity to drill down a bit, at some point, into what are the reasons for that. Thank you.

DR. LO RE: Other questions, clarifying questions?

(No response.)

DR. LO RE: One of the questions that I had, there was a note -- I think, Dr. Crist, this was in

your presentation -- that within the 7-day window, 80-to-85 percent who can become pregnant pick up their initial prescription typically within the median of 2 days; mean 2.3 to 2.4.

I just wanted to get a sense perhaps from IPMG, are there any text alerts or reminders that patients are given that they need to pick up their prescription; that they are missing their window?

MR. SHAMP: Jim Shamp from UBC. There are no texts or communications to the patient that they are about to miss their window, but I'm looking for confirmation. With the introduction of the patient calendar, the patient will have access to that, and on that patient calendar, they will be able to see where they are in their window and how many days they have left.

DR. LO RE: And that calendar, if I'm correct in remembering, was recently a recommendation that was reinstated; is that correct?

MR. SHAMP: That was a proposed modification that was before FDA, and as you heard this morning,

the FDA has approved that modification, so we will be determining the best time to introduce that back into the system.

DR. LO RE: An operationally, how does that look that calendar? How does a patient actually use that? Is that something on their smartphone? Is it web-based?

MR. SHAMP: Slide up. This is Jim Shamp from UBC. This is an image of the calendar as you would see it in the website, so it is website based. The website can be used on your iPhone. We do not have a specific app for the phone, but you can certainly access the website from your as well.

It's probably very difficult to see, but it shows you the days of your 7-day window and specifically where you are as far as completing your requirements and how many days you would have left, once you've satisfied all your requirements, to pick up that prescription. Thank you.

DR. LO RE: Great. Thank you very much.

Follow-up question, Dr. Green?

DR. GREEN: Yes. You actually sort of just

raised something along these lines. No one goes to websites anymore. We go to websites to chat [indiscernible]. Everyone does everything on their phone. If it would be possible to develop an app, even for the simple thing of answering the questions, something like that, I don't know if that's something anybody -- IPMG -- would be willing to entertain, but I think it would make life much easier. Again, no one goes to websites anymore when they can do it on their phone through an app.

Is that something you would be willing to entertain?

MR. SHAMP: Jim Shamp from UBC. We appreciate your thinking on that, and that is certainly something we can discuss with the agency. Thank you.

DR. GREEN: Thank you.

DR. LO RE: Great.

Dr. Woodward?

DR. WOODWARD: Hi. Maria Woodward. Along those same line for ease of use, is it possible to

even have that calendar as a printout so the key dates are available as something that can be printed out for patients, or even within that calendar function, key dates could be added to people's calendars? That's sort of for higher level, but having some method that the patient doesn't have to go back and can look as a printout, or within reminder systems for ease of use, because app development I know can take a long time. But I agree it would be very helpful for users at that level.

MR. SHAMP: Jim Shamp from UBC. My understanding is that the calendar is printable as it is today, and it's an interesting idea to add functionality into that to allow you to add this to your calendar on your phone. We'd certainly take that back and discuss it with the sponsors and see if that is something that can be implemented. Thank you.

DR. WOODWARD: Thank you.

DR. LO RE: Great.

Other clarifying questions for either the

agency or for IPMG?

(No response.)

Adjournment

DR. LO RE: Alright. If no other, we will be able to give you approximately 15 minutes of your time back.

I just want to compliment both those at IPMG and at the agency for the excellent presentations and the care with which you have all responded to all of our questions. Speaking on behalf of the advisory committee, it was very appreciative.

If there are no further questions, we'll adjourn this first day of this two-day meeting. We're going to start day 2 tomorrow promptly at 10 a.m. Eastern Daylight Time. Panel members, please remember there should be no discussion of the meeting topics with other panel members until we reconvene tomorrow. Day 1 is now adjourned. Thanks, everybody.

(Whereupon, at 3:44 p.m., the meeting was adjourned.)