Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee March 28-29, 2023

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined the advisory committee meeting via an online video conferencing platform

Topic: The committees discussed proposed changes to the iPLEDGE Risk Evaluation and Mitigation Strategy (REMS) requirements to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of isotretinoin oral capsules for patients.

These summary minutes for the March 28-29, 2023 joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) of the Food and Drug Administration were approved on June 12, 2023.

I certify that I attended this meeting and that these minutes accurately reflect what transpired.

/s/	**/s/**
Philip Bautista, PharmD, MPH	Vincent Lo Re III, MD, MSCE
Designated Federal Officer, DSaRM	Chairperson, DSaRM

Summary Minutes of the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee
March 28-29, 2023

The **Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee**, Center for Drug Evaluation and Research, met jointly on March 28-29, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and IPMG. The meeting was called to order by Vincent Lo Re III, MD, MSCE. The conflict-of-interest statement was read into the record by Philip Bautista, PharmD, MPH (Designated Federal Officer). There were approximately 909 people viewing on day 1, and 716 people viewing on day 2. There was a total of four Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:
The committees discussed proposed changes to the iPLEDGE Risk Evaluation and Mitigation Strategy (REMS) requirements to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of isotretinoin oral capsules for patients.

Attendance:

Drug Safety and Risk Management Advisory Committee Members (Voting):
Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Sascha Dublin, MD, PhD; John B. Hertig, PharmD, MS, CPPS, FASHP; Collin A. Hovinga, PharmD, MS, FCCP; Krista F. Huybrechts, MS, PhD; Tao Liu, PhD; Vincent Lo Re III, MD, MSCE (*Chairperson*); Mara McAdams DeMarco, MS, PhD; Suzanne B. Robotti (*Consumer Representative*)

Drug Safety and Risk Management Advisory Committee Member Not Present (Voting):
James Floyd, MD, MS; Lewis S. Nelson, MD

Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting):
Reema J. Mehta, PharmD, MPH (*Industry Representative*)

Dermatologic and Ophthalmic Drugs Advisory Committee Members Present (Voting):
Ken Katz, MD, MSc, MCSE; Brian Green, DO, MS, FAAD; Megha Tollefson, MD; Maria A. Woodward MD MSc

Dermatologic and Ophthalmic Drugs Advisory Committee Not Present (Voting):
James Chodosh, MD, MPH (*Chairperson, Ophthalmology*); Todd Durham, MS, PhD (*Consumer Representative*); Mary Elizabeth Hartnett, MD, FACS, FARVO; Timothy Murray, MD, MBA, FACS; Christina Y. Weng, MD, MBA

Dermatologic and Ophthalmic Drugs Advisory Committee Member Present (Non-Voting): Jay Horrow, MD, MS, FACC (*Industry Representative*)

Temporary Members (Voting):
Abbey Berenson MD, PhD; David A. Chambers, DPhil; Edward W. Cowen, MD, MHSc; Kort Delost, RPh; Sonia Hernandez-Diaz, MD, DrPH; Donna Ludwinski, BSChE (*Patient Representative*); Sonja A. Rasmussen, MD, MS; Brian Salvas, PharmD; Courtney A. Schreiber, MD, MPH

FDA Participants (Non-Voting):
Claudia Manzo, PharmD; Cynthia LaCivita, PharmD; Jacqueline Sheppard, PharmD; Leyla Sahin, MD; Tatiana Oussova, MD, MPH; SeVan H. Kolejian, PharmD, MBA, BCPPS

Designated Federal Officer (Non-Voting): Philip A. Bautista, PharmD, MPH

Open Public Hearing Speakers Present:
Emmy Graber, MD, MBA and Andrea Zaenglein. MD, FAAD (American Acne & Rosacea Society); Robert Sidbury, MD (Society for Pediatric Dermatology); Ealena Callender, MD, MPH (National Center for Health Research); Ilona Frieden, MD, FAAD and John Barbieri, MD, FAAD (American Academy of Dermatology Association)

The agenda was as follows:

<u>Day 1: March 28, 2023</u>:

Call to Order	**Vincent Lo Re III, MD, MSCE** Chairperson, DSaRM
Introduction of the Committee Conflict of Interest Statement	**Philip Bautista, PharmD, MPH** Designated Federal Officer, DSaRM
FDA Opening Remarks	**Cynthia LaCivita, PharmD** Director, Division of Risk Management (DRM) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Isotretinoin Background & Regulatory History	**Roselyn E. Epps, MD, FAAP, FAAD** Clinical Reviewer Division of Dermatology and Dentistry Office of Immunology and Inflammation Office of New Drugs (OND), CDER, FDA
Overview of the iPLEDGE REMS	**James Shamp** VP of Data Intelligence and Program Analytics

	United BioSource Corporation (UBC)
IPMG Overview of Pregnancy Registry	**Sara Ephross, PhD** Senior Director, Epidemiology Syneos Health
Contraception and Pregnancy Testing Requirements to Prevent Exposure in Pregnancy	**Wenjie Sun, MD, FACOG** Clinical Reviewer Division of Pediatrics and Maternal Health Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine OND, CDER, FDA
IPMG Modifications to iPLEDGE REMS Program	**Gregory P. Wedin, PharmD** Pharmacovigilance and Risk Management Director Upsher-Smith Laboratories, LLC
Clarifying Question to Presenters	
LUNCH	
Potential Modifications to the iPLEDGE REMS	**Lindsey Crist, PharmD, BCPS** Risk Management Analyst DRM, OMEPRM, CDER, FDA
Clarifying Question to Presenters	
ADJOURNMENT OF DAY 1	

Day 2: March 29, 2023:

Call to Order	**Vincent Lo Re III, MD, MSCE** Chairperson, DSaRM
Introduction of the Committee	**Philip Bautista, PharmD, MPH** Designated Federal Officer, DSaRM
FDA Opening Remarks	**Cynthia LaCivita, PharmD** Director, Division of Risk Management (DRM) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE) CDER, FDA
OPEN PUBLIC HEARING	
LUNCH	

Questions to the Committee/Committee Discussion

ADJOURNMENT OF DAY 2

Questions to the Committees:

1. **VOTE:** The REMS currently requires a 19-day lockout period for patients who can become pregnant and do not pick up their first prescription of isotretinoin within the 7-day prescription window.

   Should the iPLEDGE REMS retain the 19-day lockout period requirement before patients can take an additional pregnancy test to be eligible to receive isotretinoin?

   a. Yes
   b. No

   If you voted "No", please provide your rationale and recommendations on when the additional pregnancy test should occur before starting treatment.

   Vote Result: Yes: 4 No: 17 Abstain: 1

   Committee Discussion*: The majority of the members (4 Yeses, 17 Noes, 1 Abstention) voted "No" to the question as to whether the iPLEDGE REMS should retain the 19-day lockout period requirement before patients can take an additional pregnancy test to be eligible to receive isotretinoin. Overall, the majority of members agreed that the 19-day lockout period was arbitrary, not aligned with knowledge of fertility cycles and known risks for different patients, and too burdensome, especially on patient populations with low resources. These members recommended that patients be allowed to take a pregnancy test immediately if they miss the 7-day prescription pickup window and be allowed to pick up their medication after they demonstrate a negative pregnancy test result. They also recommended that the IPMG and FDA monitor monthly pregnancy rates after this change is made. The 4 members who voted "Yes" stated that the 19-day lockout period has demonstrated to prevent fetal exposure and argued that there was no evidence to support a change to the requirement. The one member who abstained stated that there was neither enough data to support the current requirement or inform changes to this requirement. Overall, the members agreed that more data are needed as to why patients miss the 7-day prescription pickup window which could help inform future changes. Please see the transcript for details of the Committees' discussion.*

2. **DISCUSSION**: Discuss whether the REMS should require pregnancy tests be completed in a medical setting (e.g., office, laboratory) rather than at home.

   ***Committee Discussion**: Overall, the members agreed that the REMS should allow for home pregnancy tests in addition to tests in a medical setting (e.g., office, laboratory). They stated that this would increase access to the medication, especially for patient populations with low resources. They stated that there are no data to compare the performance of pregnancy tests completed in a medical setting to tests completed at home. Given the rise of telemedicine, the members agreed that home pregnancy tests are feasible, and they recommended that the REMS include methods to prevent fraudulent home testing results, such as requiring names, dates, bar codes, and uploading tests results to the iPLEDGE system. The committee agreed that there was no observed increase in fetal isotretinoin exposure during the COVID-19 pandemic when at home pregnancy tests were allowed. They also acknowledged that the situational context during the COVID-19 pandemic and post-pandemic are different and may not be directly comparable. Please see the transcript for details of the Committees' discussion.*

3. **VOTE**: For patients who cannot become pregnant, when should the REMS require the prescriber document counseling the patient in the iPLEDGE system?

   a. Only with the first prescription as part of patient enrollment
   b. Monthly (current requirement)
   c. Every 120 days
   d. Some other frequency (and provide the frequency and rationale)

   Vote Result: A: 10 B: 1 C: 6 D: 5

   ***Committee Discussion**: Overall, the members made a wide variety of recommendations regarding the requirements for prescribers to document counseling in the iPLEDGE system for patients who cannot become pregnant. The members agreed that there was a lack of data regarding the impact of prescriber documentation on risks for isotretinoin diversion and blood donation/transfusion while on isotretinoin. Ten (10) members voted that the REMS should only require prescribers to document counseling patients who cannot become pregnant with the first prescription as part of patient enrollment. These members agreed that the risks for diversion or sharing isotretinoin and the risk of exposure to isotretinoin through blood/donation/transfusion are low. Some of these members added that while counseling is needed, documentation is unnecessary and overly burdensome. One of these members stated that the risk for blood donation or transfusion is low since blood donation clinics screen for teratogenic drugs, including isotretinoin. One member voted that the requirement should remain the same because there was no data to inform a change. Six members voted that the requirement should be switched to every 120 days with two of these members commenting they were comfortable with documentation only at treatment initiation. Five members voted that the requirement should be changed to another frequency. Some members recommended a range of frequencies from every 90 days to six months. Others stated that they could not recommend a specific frequency due to lack of data; they agreed that the current requirement*

is too burdensome. Two members commented they were comfortable with documentation only at treatment initiation. Overall, these members agreed that patients receive sufficient information when prescribed a new medication and that additional counseling might be necessary especially for patients who have prolonged treatment. Please see the transcript for details of the Committees' discussion.

4. **DISCUSSION**: The iPLEDGE Pregnancy Registry collects information on fetal exposure, pregnancy outcome, fetal outcome, and root cause analysis. Discuss recommendations on the pregnancy registry requirement and ways in which it could be streamlined to encourage more participation to yield high quality data.

   ***Committee Discussion**: Overall, members agreed it is not necessary to continue to collect "follow-up data" (i.e., pregnancy and fetal outcome information) and that more effective communication and transparency are needed regarding how patients' data will be used if they participate in the iPLEDGE Pregnancy Registry. The members recommended text pushes and more user-friendly platforms to increase participation. They also recommended that participation in the registry should be the default with patients being given the option to opt out. Given the current context regarding pregnancy terminations and policy differences between states, the members recommended clearer assurances of patient confidentiality and avoiding questions about patients' intentions to terminate their pregnancy. The members also recommended collecting data as to why patients are not participating in order to inform improvements. Finally, the members agreed that information on root cause analysis should be prioritized. They recommended that additional data, regarding reasons for contraception failures be collected (e.g., qualitative, more specific and additional context). Please see the transcript for details of the Committees' discussion.*

5. **DISCUSSION**: Discuss any additional recommendations to minimize burden in the iPLEDGE REMS.

   ***Committee Discussion**: The members proposed a wide range of recommendations to minimize burden in the iPLEDGE REMS. Some members recommended that a mobile application be created to improve access to the system, especially by younger patients. Another member recommended that the REMS systems be re-integrated into pharmacy dispensing systems to prevent pharmacy operation disruptions that have occurred since the recent vendor change. Another member recommended that, in addition to prescribers, other members of the health care team (e.g., nurses and pharmacists) be allowed to provide documented counseling in order to share REMS burden. Another member recommended that the REMS be changed to lower burden on patients currently on user independent methods such as long-acting reversible contraceptives (LARC), which have higher effectiveness. Another member recommended more explicit information on emergency contraception counseling for prescribers and patients. One member stated that emergency contraception should be made readily available for patients who choose abstinence or oral birth control given their higher risk for pregnancy. Members also recommended that IPMG engage regularly and transparently with stakeholders in order to obtain feedback and inform*

improvement. They also recommend that IPMG collect data in a way that allows analysis of health disparities. Please see the transcript for details of the Committees' discussion.

The meeting was adjourned at approximately 3:15 p.m. ET on March 29, 2023.