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Robert M. Califf, MD
Commissioner of Food and Drugs
Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD, 20993

Cynthia LaCivita, PharmD
Director
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10903 New Hampshire Ave
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RE: FDA-2023-N-0573-0002 Changes to Third-Party Vendors for Risk Evaluation and Mitigation Strategies; Establishment of a Public Docket; Request for Comments

Dear Commissioner Califf,

Thank you for the opportunity to provide written comments on the Food and Drug Administration (FDA) request for public comment on factors that the FDA should consider when it reviews a proposed risk mitigation and evaluation strategy (REMS) modification request that are prompted by or related to a change in a REMS administrator for a REMS with certain elements to assure safe use (ETASU).[1] As the leading society for dermatological care, the American Academy of Dermatology Association (AADA) takes every opportunity to weigh in on matters that impact our members and their patients.

The AADA represents more than 17,000 dermatologists nationwide. Our members are committed to excellence in the medical and surgical treatment of skin disease, advocating for high standards in clinical practice, education, and research in dermatology and dermatopathology, and driving continuous improvement in patient care and outcomes while reducing the burden of skin disease.[2]

[1] https://www.regulations.gov/document/FDA-2023-N-0573-0002
[2] https://www.aad.org/about-aad

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Stakeholder input from physicians is crucial for any REMS modification, as they play a key role in ensuring that isotretinoin products, are prescribed and used safely by patients. Physicians had to grapple with the adverse effects of hasty and seemingly capricious alterations to a REMS system. Physicians should not have to overcome this much adversity in obtaining the medications patients require when the REMS system proves inadequate.

The AADA believes that FDA should require stakeholder input from prescribers at all stages of developing, implementing, and tracking a REMS modification related to changes to third party vendors. Specifically, the AADA recommends that the FDA require drug sponsors and their REMS administrators to:

- Test proposed changes to REMS system prior to implementation with a group of end users including physicians, patients, and pharmacists;
- Allow for ample time for stakeholders to transition to a new platform including beta-testing that platform to assure it is as glitch-free as possible;
- Improve support services for prescribers when there is REMS System failure; and
- Facilitate greater transparency between drug sponsors, REMS administrators, and stakeholders, including a named point of contact for key stakeholders and including stakeholders in the decision-making process.

Background: Isotretinoin & iPLEDGE REMS Program

Isotretinoin is used to mitigate severe scarring and relieve the psychosocial stigma associated with nodulocystic acne. It is also used off-label to treat patients with a variety of other serious skin conditions such as ichthyoses, cutaneous T-cell lymphoma, patients at high risk for skin cancer, disfiguring skin conditions due to chemotherapy, and childhood neuroblastoma.

Isotretinoin is subject to a risk evaluation and mitigation strategy (REMS) managed through the iPLEDGE REMS program. The iPLEDGE REMS program goals are to manage the risk of isotretinoin's teratogenicity, to minimize the risk of fetal exposure isotretinoin, and to inform prescribers, pharmacists, and patients about isotretinoin's serious risks and safe-

use conditions.[3] While the AADA recognizes the absolute need to prevent fetal exposure, the burdensome administrative requirements for the complex iPLEDGE REMS program leads to inadvertent harms that decrease access to isotretinoin and promote healthcare disparities.

On December 13th, 2021, the Isotretinoin Products Manufacturing Group (IPMG) implemented FDA-approved modifications, including iPLEDGE REMS system changes for health care professionals and patients. The system update led to numerous technical difficulties experienced by physicians, patients, and pharmacists, resulting in unnecessary and negatively life-altering disruptions to patient care. IPMG could have prevented this by involving dermatologists early in its process for developing iPLEDGE changes.

AADA's Recommendations for Proposed Modifications to REMS

Unfortunately, since the system update in 2021, Dermatologists continue to face significant challenges with navigating the system requirements of the iPLEDGE REMS program, resulting in decreased patient care, and increased administrative burdens on clinical practices. Furthermore, the lack of clear and accessible communication from IPMG regarding iPLEDGE changes and prescriber support interferes with optimal care for patients.

The AADA strongly urges FDA to exercise its regulatory authority to encourage IPMG to seek stakeholder input when it makes updates or changes to the iPLEDGE REMS system and on an ongoing basis to ensure optimal functioning of the program. Below are AADA's key recommendations for proposed REMS modifications related to changes in third party vendors and other system updates from drug sponsors and their REMS administrators.

A. The FDA Should Require Drug Sponsors and Their REMS Administrators to Test Changes to REMS System Prior to Implementation.

Input from multiple stakeholders and beta testing with prescribers, pharmacists, and patients when there are significant changes in the technologic workflows and upgrades to a REMS system will improve user experience with the platform and prevent access issues for

[3] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/ipledge-risk-evaluation-and-mitigationstrategy-rems?utm_medium=email&utm_source=govdelivery

patients. Also, beta testing allows REMS administrators to identify and resolve any technical issues and user frustrations with the new system before implementation of major changes to the platform.

During the iPLEDGE REMS system update, dermatologists and pharmacists had significant problems with merging user data from the previous system into the new one. The system was not designed to be feasible in current clinical workflows (e.g. assuming a pregnancy test would be available at the time of consent, even though these usually cannot be completed until after the visit as many dermatology practices do not have the capabilities to conduct pregnancy testing on site). In addition, there were concerns about how the new website would function and whether there would be adequate call center capacity to address any acute issues. Despite numerous pleas from AADA to collaborate with the IPMG for a seamless rollout, our proactive offers to join forces were disregarded.

Unfortunately, as we had warned, the rollout of the new system was problematic. Due to merging issues, many dermatologists and active patients became unable to access their accounts. This issue was compounded by iPLEDGE support staff being ill-equipped to address the sheer call volume of clinicians, pharmacists and patients who were inadvertently disenrolled from the program, with call wait times lasting over 8 hours if callers were able to get through at all. In addition, for unclear reasons the calendar feature was not carried over to the new platform which caused confusion among our members, and thus, a patient's access to isotretinoin. Without access to medication, many patients had treatment disruptions and were put at increased risk for treatment failure and prolonged exposure to this teratogenic medication.

If there was initial testing and assurance of a smooth transfer of REMS data to the new system, IPMG would have avoided problems with basic website functionality, patient and prescriber disenrollment, and call center service issues. *Therefore, AADA recommends that FDA require drug sponsors and REMS administrators to conduct real world testing of the proposed changes to the REMS system prior to full implementation.*

B. The FDA Should Require Drug Sponsors to Give Physicians and Other Stakeholders Ample Time for Stakeholders to Transition to a New Platform.

Physicians and other prescribers need sufficient time to transition to a new REMS system. In the case of isotretinoin, dermatologists, pharmacists, and their patients faced several challenges during the rushed roll out of the new iPLEDGE System. Although IPMG notified prescribers of the system update in October 2021, prescribers were not given adequate time to prepare for a system shut down, patient and physician disenrollment in the program, and the extremely high call volume at the iPLEDGE help center. Furthermore, IPMG did not share a rationale for modifications to the platform, solicit stakeholder input, or test any of the proposed changes with isotretinoin prescribers.

Providing a mere two months' notice without soliciting any input from prescribers or conducting thorough testing of the proposed change is not enough time and is egregious. Not only were physicians ill-prepared to use the new system, IPMG was unable to handle the call volume from physicians, pharmacists, and patients requesting assistance. Furthermore, hundreds of patients were in jeopardy of losing access to vital treatments due to basic system problems. *Therefore, the AADA recommends that FDA require REMS administrators and drugs sponsors to give at least 12 months' notice of a future REMS change to allow for sufficient pilot testing of system changes prior to full rollout and ample time to adequately prepare prescribers and patients to transition stakeholders from one REMS system to another REMS system.*

C. The FDA Should Encourage Drug Sponsors and REMS Administrators to Improved Their Support Services when a REMS System Fails.

At the time of migration to a new system, there were little remedies for dermatologists reporting system failures or challenges with the new platform. In the early phase of the new platform, the AADA made a request to IPMG for direct access to their leadership to discuss potential workarounds for iPLEDGE system failures, like allowing the use of a downloadable patient consent form, available on the public side of the iPLEDGE website. This would have prevented several patient and prescriber difficulties with completing the requirements of the program during the initial system failure. However, after being promised a direct point of contact, the AADA received a generic email address that went to staff at the call center. Even to this day, we do not have a dedicated point of contact readily available to address our concerns.

Furthermore, some AADA members shared that they, their staff, or their patients were erroneously removed from the program. For example, an AADA member was in communication with IPMG for several months to rectify a compliance issue. Despite her numerous attempts to share the required paperwork and meet any additional requests, she was punitively deactivated from the program for a clerical error with little no recourse for a decision made by IPMG. Issues like this can be resolved by having a consistent and responsive point of contact for prescribers' compliance questions or additional support services for providers experiencing a REMS system failure.

Accordingly, the AADA recommends that the FDA provide additional support from drug sponsors and REMS administrators in improving their support services for prescribers having trouble with a REMS platform.

D. The FDA Should Facilitate Greater Transparency between REMS Administrators, Drug Sponsors, Patients and Physicians.

There is an urgent need for transparent, open dialogue between key stakeholders, including IPMG, FDA, and prescribers. Prior to the FDA's joint advisory meeting for iPLEDGE, the AADA was unable engage in meaningful dialogue with IPMG and drug sponsor representatives to discuss our members ongoing challenges with the system and share proposals to improve the iPLEDGE REMS program.

Yet, in early 2022, the AADA learned that IPMG frequently shared important data with the FDA, such as call center wait times, the number of prescriptions being filled daily, and the number and percentage of patients, pharmacists, and prescribers able to login successfully to the system. IPMG was able to compare this data to statistics prior to the platform launch. This type of data should be shared transparently with all stakeholders so that we can determine whether temporary programmatic workarounds are successful, and if the iPLEDGE platform aids in the safe use of isotretinoin.

The AADA fervently believes that only through collaborative discussions can the iPLEDGE REMS program achieve necessary balance of mitigating the risk of fetal exposure and ensuring reliable, safe patient access to isotretinoin. *We strongly advocate for continued and transparent communication between IPMG and dermatologists, including identifying a consistent point of contact for prescriber grievances and compliance issues*. In addition, the

AADA reiterates its previous recommendation to include additional key stakeholders such as physicians and pharmacists during meetings between the FDA and IPMG when they are considering changes to the iPLEDGE REMS program and any future iPLEDGE REMS program modifications.

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On behalf of the American Academy of Dermatology's membership, representing dermatologist across the country, we thank you again for allowing the public to provide input on future REMS modifications and changes related to third-party vendors. We look forward to working with the FDA to ensure our patients have timely and safe access to life-changing treatments. To discuss this matter further or schedule a meeting, please have your staff contact Stephanie Croney, JD, American Academy of Dermatology Association's Assistant Director of Regulatory Policy at scroney@aad.org or via phone at 202-712-2612. Thank you for your time and consideration.

Sincerely,

Terrence A. Cronin Jr., MD, FAAD
President