January 27, 2022

The Honorable Patty Murray
Chairwoman
Senate Health, Education, Labor, and Pensions Committee
Washington, DC 20510

The Honorable Richard Burr
Ranking Member
Senate Health, Education, Labor and Pensions Committee
Washington DC, 20510

Dear Chairwoman Murray and Ranking Member Burr:

On behalf of the undersigned organizations, we would like to express our concern about the recent modifications of the Risk Evaluation and Mitigation Strategies (REMS) for clozapine and isotretinoin required by the Food and Drug Administration (FDA). The manner in which the changes to these REMS were undertaken resulted in unnecessary disruptions to patient care. In the case of those receiving clozapine, this disruption could prove to be life-threatening. In the case of those receiving isotretinoin, the disruptions are both distressing and negatively life-altering.

The changes in the REMS affect multiple steps in the patient care process from enrollment in the programs to prescribing, monitoring, dispensing, obtaining medications, and receiving reimbursement. The concerns we have heard from our members have been remarkably consistent across our organizations.

***We recommended to FDA that both the REMS be suspended immediately and undergo thorough reviews. These reviews should be designed to inform the FDA and manufacturers of the problems the REMS present and potential strategies to remedy these issues. More importantly, these reviews should weigh the potential harm of the elements of the REMS and the REMS themselves against the potential benefits that the REMS may bring. Congress should also hold hearings to understand the problems with the REMS planning, rollout, and implementation and develop recommendations to improve future REMS programs.***

**Clozapine**

Clozapine presents a textbook case of why REMS must be carefully developed and tested. Clozapine is a potentially lifesaving medication for patients living with schizophrenia who have not responded to other medications. An interruption in treatment could result in a patient relapse with devastating effects including hospitalization, suicide attempts and even violent acts. Furthermore, the interruption may lead to an inappropriate regimen for restarting clozapine. This could result in a life-threatening reaction such as a dramatic fall in blood pressure and/or slowing of the heart rate. Clozapine is available generically, so expense is not an issue in its use. Experts in the treatment of schizophrenia are unanimous in their conclusion that clozapine is underutilized. Data shows that the rate of clozapine use is much lower in the United States in comparison to many other countries. However, the stringent elements of the REMS are seen as barriers to clozapine use.

The new Clozapine REMS launched on November 15 presented challenges to prescribers, pharmacists, and healthcare systems. The excessive workload, incompatibility with normal healthcare workflow, rushed implementation and failure to adequately test the system led some providers to stop prescribing it and some pharmacies to stop dispensing it, making access to this underutilized treatment more difficult for an already vulnerable population. The REMS puts additional strain on a health care

workforce already under immeasurable stress from COVID-19, including pharmacists trying to meet the demands of influenza and pneumococcal vaccinations, COVID-19 vaccinations, boosters, and testing and the country contending with another surge from the Omicron variant. The rollout of this REMS modification was so flawed the FDA had to cease elements of the program on November 19 just four days after it was implemented.

Over a month after the launch of the Clozapine REMS, we continue to hear from our members about problems. We do appreciate the multiple listening sessions that the FDA held with concerned organizations since the launch of the new REMS and their temporary suspension of certain Clozapine REMS requirements for 90 days. However, this suspension will end in mid-February, and we are concerned more issues will arise. And, while we applauded the temporary suspension, it also resulted in unforeseen complications due to its complexity. Suddenly, many pharmacies found they were unable to obtain insurance approval and reimbursement for dispensing clozapine to patient who had been receiving the medication for years.

**Isotretinoin**

Isotretinoin is used to mitigate severe scarring and allay the psychosocial stigma associated with nodulocystic acne. It is a highly effective, and commonly used treatment for severe and refractory acne vulgaris, but also used off-label to treat patients with a variety of other serious skin conditions such as ichthyoses, cutaneous T-cell lymphoma, patients with multiple skin cancers used for skin cancer prevention, acneiform eruptions due to chemotherapy, and childhood neuroblastoma, among others. The abrupt halting of therapy may worsen a patient's skin disease. This REMS program has been in existence for 15 years and it has many flaws. The most egregious of these is that although its primary objective is to decrease fetal exposure to Isotretinoin, it has equal monthly attestation requirements for individuals who cannot become pregnant. This has led to health disparities and – compared to other countries without this REMS program - to the use of higher doses of the medication, with attendant higher side-effect risks in an attempt to finish courses of the medication as quickly as possible and exit the REMS program.

Added to these long-standing problems, on December 13$^{th}$, a new iPLEDGE REMS launched for Isotretinoin, with similar issues to the Clozapine REMS, including access issues preventing patients, prescribers, and pharmacists from logging in, problems with basic website functionality stemming from rushed implementation and inadequate testing of the system, and call center service issues with wait times being 4-8 hours if callers were able to get through at all that further compounded these issues.

We are deeply concerned that almost identical issues were experienced in the two REMS a month apart. The sole purpose of the iPLEDGE REMS program is avoidance of fetal exposure to Isotretinoin. Given the mandate of the iPLEDGE REMS program, Isotretinoin scripts are available for only one month, with no refills. With every passing day, thousands of patients are unable to obtain the medication. After 30 days, isotretinoin will be completely unavailable for many patients in need. Patient safety has been compromised by the dysfunctional platform, including prolonging the interval for exposure, causing higher relapse with increased risk of scarring, increasing time reliant on combined oral contraceptives and other methods of contraception. The lack of accountability, transparency, and responsibility by the program sponsors and platform administrators has and will continue to disrupt and compromise patient care. The downstream effect is physician offices are being inundated with patient phone calls, messages via electronic messaging portals, which is limiting the capabilities to care for other patients.

Since the December 13 rollout of the iPLEDGE REMS program for Isotretinoin, the IPMG has made some efforts to address concerns, but their proposed changes are being done in a piecemeal fashion and they do not address the scope and severity of the issues at hand. We appreciate that the FDA directed the IPMG to collaborate with stakeholders as they are ultimately responsible for the program. However, there have been no responses from either the IPMG or FDA to the proposed solutions advanced by physician and pharmacists to restore access. A request was made to IPMG for direct access to their leaders to discuss these problems, but after being promised a direct point of contact, received a generic email address which goes to staff at the call center. It is unacceptable that after all these weeks of effort by physicians and pharmacists towards a workable solution, there remains no effective path forward to work with us to resolve the situation.

**REMS Programs**

The concerns of Psychiatrists, Dermatologists, Pharmacists, Nurses, Public Health Officials and Patient Advocates about the REMS are remarkably similar:

- Design of a program affecting patients and healthcare providers without mandated input from healthcare clinicians.
- Implementation without real world testing by healthcare clinicians, systems, and payers to discover unanticipated consequences.
- Introduction of REMS elements that have not been scientifically demonstrated to improve patient safety.
- Inadequate staffing of centers running the REMS resulting in excessive wait times for patients and healthcare providers (at times more than nine hours).
- Lack of transparency into decisions regarding the REMS and failure to answer provider and stakeholder questions in a timely manner.
- Lack of uniformity in the way that REMS are designed and implemented such that hospitals, clinics and pharmacies that use medications with REMS must deal with a different system for each of the over sixty medications with REMS.

When poorly designed and executed, Risk Evaluation and Mitigation Systems are not benign. They can pose risks to patients, increase the burden on healthcare providers, provide false reassurances of safety, and raise healthcare costs. In the case of these two medications, our professional, advocacy and state governmental associations have concluded that the risks, cost, and burden of the REMS exceed any potential benefits they provide. In fact, as implemented, the REMS are not safeguarding patients; they are disrupting treatment, placing patients at risk, and making necessary treatment less accessible. We urge you to hold hearings to shine light on these issues and to identify how the REMS process may be improved and if congressional changes are needed. We also urge you to request FDA halt the two REMS programs until a thorough review of the programs is completed to reduce disruptions to treatment.

Thank you for your consideration. Please let us know if you have questions or need more information.

Sincerely,

American Academy of Dermatology Association

American Psychiatric Association

American Psychiatric Nurses Association

ASHP

College of Psychiatric and Neurologic Pharmacists

National Alliance on Mental Illness

National Council for Mental Wellbeing

CC Rachel Levine, M.D., Assistant Secretary for Health, Department of Health and Human Services

Miriam Delphin-Rittmon, Ph.D. Assistant Secretary for Mental Health and Substance Use, Department of Health and Human Services

Patrizia Cavazzoni, M.D., Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration