United States Senate
WASHINGTON, DC 20510

February 22, 2016

Dr. Stephen Ostroff, M.D.
Acting Commissioner
United States Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Dear Acting Commissioner Ostroff,

We are writing to request that FDA use its authority to require immediate-release (IR) opioids be subject to a Risk Evaluation and Mitigation Strategy (REMS). FDA currently only subjects extended-release and long-acting (ER/LA) opioid analgesics to REMS. While we applaud a REMS requirement for ER/LA opioids, they only make up nine percent of all opioids prescribed compared to IR opioid analgesics, which make up 91 percent of all opioids prescribed.[1] Furthermore, prescriptions for IR opioids increased from 164.8 million in 2000 to 234 million in 2009.[2] With IR opioids making up over 90 percent of all opioids prescribed, it make sense that they should be subject to a REMS.

As you know, FDA's decision to limit the opiate REMS to ER/LA formulations was controversial. At the time, many critics argued that failing to include IR formulations could imply they were safer and could lead to a preference for prescribing them.[3] In response, FDA argued that ER/LA opioids were responsible for a higher number of emergency room visits for nonmedical use of opioids and presented a magnified risk of overuse and death.

We would like to highlight that this decision has put FDA at odds with two of its own advisory committees. According to an article published by *Mayo Clinic Proceedings*, a joint meeting between FDA's Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee discussed REMS for opioids in 2010. During their discussions, both committees "believed that [REMS] should be mandatory for all opioids, not just the ER/LA opioids." Both Committees reasoned that "the public health concern was related to misuse and abuse of all opioids and as such warranted a universal approach to both

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[1] Food and Drug Administration, *Outpatient Prescription Opioid Utilization in the U.S., Years 2000-2009*. 22 July, 2010.
[2] Ray, James B. *Implications of the Extended-Release/Long-Acting Opioid REMS for Managed Care*, American Journal of Managed Care (Aug. 2015).
http://www.ajmc.com/journals/supplement/2015/ace0029_aug15_painrems/ace0029_aug15_painrems_ray
[3] *Id.*

extended and immediate-release opioid preparations."[4] This consensus by both FDA advisory committees was ultimately ignored by FDA.

We request that the FDA reverse its decision and follow the recommendations of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee by expanding the ER/LA opioids REMS requirement to IR opioids. If FDA chooses to continue not requiring REMS for IR opioids, we request more information as to its decision to contradict its own advisory committees and data that indicates "weak or insufficient evidence" in determining an increased risk of overdose, addiction, abuse, or misuse in ER/LA opioids over IR opioids.[5]

In 2012, we saw a drop in painkiller prescribing rates, and not surprisingly, a subsequent drop in prescription drug deaths for the first time since the 1990s.[6] The clear link between opioid prescribing practices and the acceleration of this pernicious epidemic, along with the damage from opioid misuse and abuse to individuals, families, communities, and our nation as a whole cannot be overstated. We understand that battling the misuse and abuse of prescription drugs on our society is a task that requires a long-term and comprehensive approach. We also understand that FDA will play an immensely important role in achieving this ambitious but necessary goal of putting a stop to opioid abuse, misuse, and death in this country. We look forward to hearing back from you regarding an expansion of a REMS requirement all opioids, including immediate-release opioids, as soon as possible.

Sincerely,

RICHARD BLUMENTHAL
United States Senator

JOE MANCHIN III
United States Senator

ANGUS KING
United States Senator

KIRSTEN GILLIBRAND
United States Senator

[4] Brooks, Marta J. *Mitigating the Safety Risks of Drugs with a Focus on Opioids: Are Risk Evaluation and Mitigation Strategies the Answer?*, Mayo Clinic Proceedings (Dec. 2014) http://www.mayoclinicproceedings.org/article/S0025-6196(14)00794-0/fulltext.

[5] Agency for Healthcare Research and Quality. *The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain* (Sep. 2014). http://www.ncbi.nlm.nih.gov/books/NBK258809/.

[6] Centers for Disease Control and Prevention. "Injury Prevention & Control: Prescription Drug Overdose" (Aug. 25, 2015). http://www.cdc.gov/drugoverdose/data/.

EDWARD MARKEY
United States Senator

CHISTOPHER S. MURPHY
United States Senator