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August 17, 2018

The Honorable Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Gottlieb,

I write to seek an update on the U.S. Food and Drug Administration's (FDA) efforts to administer, monitor, and analyze the Risk Evaluation and Mitigation Strategy (REMS) for prescription opioids. I am specifically concerned about a recent *New York Times* article indicating that for years, the FDA ignored red flags generated by the REMS for transmucosal immediate-release fentanyl (TIRF) products that revealed possible inappropriate prescribing of these drugs, placing patients at risk of addiction and overdose.[1]

As part of the drug approval process, the FDA can require a drug's manufacturer to develop and implement plans, known as REMS, to help mitigate the risks associated with the drug's approval. REMS generally consist of actions the drug manufacturer must take, which can include prescriber education and patient registries, to help ensure that the drug is prescribed and used appropriately. The FDA reviews and approves REMS, and maintains broad authority to intervene in the REMS should it prove to be inadequate or insufficient in addressing public health risks.

The FDA approved TIRF products to help treat breakthrough pain for opioid-tolerant cancer patients who are prescribed another opioid for around-the-clock pain management.[2] The FDA approved REMS for the entire class of TIRF products in 2011.[2] According to the FDA, the TIRF REMS was "designed to limit use only in opioid-tolerant patients; to avoid inappropriate conversion between TIRF medicines; to reduce accidental exposure; and to educate prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose."[2]

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[1] Emily Baumgaertner, *F.D.A. Did Not Intervene to Curb Risky Fentanyl Prescriptions*, New York Times (August 2, 2018), https://www.nytimes.com/2018/08/02/health/fda-fentanyl-opioid-epidemic-overdose-cancer.html?et_rid=698403255&s_campaign=fastforward:newsletter

[2] Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's continued, careful oversight of the REMS associated with transmucosal immediate-release fentanyl products, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm615411.htm (last visited August 7, 2018)

As discussed in the *New York Times* article, the FDA obtained information that TIRF products may have been prescribed to patients for whom the medication was not indicated. An assessment of the TIRF REMS found that 42 percent of TIRF prescriptions may have been prescribed for patients who are not opioid-tolerant.[2] Another survey from 2017 found that 18 percent of TIRF prescribers and 48 percent of TIRF patients incorrectly believed that TIRF products were approved by the FDA for use in non-cancer patients.[1] Despite this information, the FDA supported an industry-proposed change to the mandatory Patient-Prescriber Agreement form, effectively removing direct assurances that TIRFs were prescribed only to opioid tolerant patients.[1]

The research and documents cited in the article also run counter to a response I received from your agency in November 2017 concerning REMS for opioid painkillers. When addressing a question as to whether REMS for both TIRF and extended-release/long-acting opioids were achieving their goals, your response stated that, "there is information that shows compliance with the [REMS] program requirements and that patient and prescriber knowledge of the risks are high."[3] This is in contrast to information presented in the *New York Times* article that indicates the FDA has for years been made aware of issues with TIRF REMS compliance.

It is concerning the manufacturers of risky prescription opioids – who stand to financially benefit from the proliferation of their products – are left to self-police the implementation of the REMS. It is even more concerning that the FDA has historically been reluctant to step-in when evidence indicates that the REMS for a product is ineffective, inadequate, or unenforced by the drug's manufacturer.

FDA cannot fulfill its role of protecting the public from the known risks of opioids if the agency is not effectively monitoring REMS performance and responding if REMS are inadequate. While I appreciate your convening of a public advisory committee to discuss the issues surrounding the TIRF REMS, it appears that a wholesale readjustment of the REMS program is necessary to fully protect patients from the dangerous side effects associated with many opioid products. To better understand your efforts to increase transparency and communication around opioid products and REMS, please answer the following questions:

1. Please provide the information from one or multiple TIRF REMS assessments that led the FDA to draw the conclusion in your November 2017 letter that prescribers and patients are knowledgeable about the risks of TIRF products.

2. In the same November 2017 response letter cited above, the FDA said the TIRF REMS consists of an Elements To Assure Safe Use (ETASU) requirement for "enrollment and certification of prescribers who prescribe for outpatient use and pharmacies, and passive enrollment of all outpatients. The program requires verification that every prescription for a TIRF product is written by a certified prescriber who has undergone training before it is dispensed to a patient."[3]

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[3] Letter from Anna K. Abram, Deputy Commissioner for Policy, Planning, Legislation and Analysis FDA to Sen. Edward J. Markey (November 1, 2017).

a. Does the FDA believe that the current training requirements through TIRF REMS are sufficient? If yes, what is the reason for the high level of inappropriate, off-label prescribing, by registered prescribers? If not, has the FDA taken any steps to change or improve the training requirements?
b. For training requirements under ER/LA REMS, what steps is the FDA taking, if any, to enhance prescriber education, either through REMS or elsewhere, to ensure prescribers are receiving adequate education on the risks of these products? To date, what percentage of prescribers have taken the education offering under the ER/LA REMS? What additional authorities could the FDA use to improve provider education?

3. In regards to information that TIRFs were prescribed to non-cancer pain patients, the *New York Times* reported that FDA officials reviewed the "piecemeal data from various stakeholders — prescriber surveys, insurance claims and industry reports" and the limited and incomplete data "made it difficult for the agency to measure potential harm to patients."[1] In your statement regarding TIRF oversight, you said that the FDA is "committed to striking a careful balance between access and safety, based on reliable evidence."[2]
    a. Upon receipt of this "piecemeal data," did FDA attempt to acquire more complete information? If not, why not? If so, what additional information was the FDA able to gather?
    b. What does the FDA consider "reliable evidence" when it pertains to assessing whether a company is adhering to its REMS and mitigating the risks of a prescription opioid?
    c. If the FDA receives information that an opioid or other drug is prescribed outside of the REMS requirements, what does the FDA do with that information? When and how is this information shared with the drug manufacturer and what steps are taken to curtail prescribing behaviors that may be harmful to public health?

4. An FDA official was quoted in the *New York Times* article as stating that more stringent oversight of the REMS program would be "extremely onerous." Given that 115 people die each day from an opioid overdose, including an overdose caused by prescription drugs, it is important that the FDA use its full authority to ensure prescription opioids are prescribed as intended, and patients and providers are well aware of the potential risks. What additional resources does the FDA need to execute this process and make compliance and assessment less onerous?

5. Since you were confirmed as the FDA Commissioner, your agency has taken several steps to improve the REMS process. For instance, you announced changes to prevent

brand name drug manufacturers from using REMS to impede generic access[4] and extended REMS requirements to immediate-release opioids.[5]

a. Is the FDA considering any future actions to further strengthen the REMS process? If so, please describe what actions and the timeline for such actions.
b. What information was shared on the August 3rd, 2018 Advisory Committee meeting that will help inform any changes the FDA may require to TIRF REMS? Is that information publicly available?

Please respond no later than September 5, 2018. Should you have any questions, please have your staff contact Nikki Hurt in my office at 202-224-2742. Thank you for your attention to my request.

Sincerely,

Edward J. Markey

Edward J. Markey
United States Senator

[4] Statement from FDA Commissioner Scott Gottlieb, M.D., on new policies to reduce the ability of brand drug makers to use REMS programs as a way to block timely generic drug entry, helping promote competition and access, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609365.htm (last visited August 7, 2018)

[5] Remarks Delivered Before FDA's Scientific Meeting on Opioids on July 10, 2017, https://www.fda.gov/NewsEvents/Speeches/ucm566189.htm (last visited August 7, 2018)