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United States Senate

SUITE SD-255
DIRKSEN BUILDING
WASHINGTON, DC 20510-2107
202-224-2742

975 JFK FEDERAL BUILDING
15 NEW SUDBURY STREET
BOSTON, MA 02203
617-565-8519

222 MILLIKEN BOULEVARD, SUITE 312
FALL RIVER, MA 02721
508-677-0523

1550 MAIN STREET, 4TH FLOOR
SPRINGFIELD, MA 01101
413-785-4610

April 21, 2016

The Honorable Robert M. Califf
Commissioner
U.S. Food and Drug Administration
Rockville, MD 20687

Dear Commissioner Califf:

I am writing to better understand how the Food and Drug Administration (FDA) administers the Risk Evaluation and Mitigation Strategies (REMS) process for prescription opioid painkillers and how FDA monitors and analyzes REMS to determine whether they are in fact protecting the public from the risks of abuse, misuse, addiction, and overdose deaths associated with opioid use.

The FDA has broad authority to require drug manufacturers to develop and implement plans, known as REMS, for drugs with serious risks. These REMS, which FDA reviews and approves, comprise a series of actions by a drug manufacturer, which are intended to lessen the risks of the drug being sold. These actions can include patient registries and direct communication to providers outlining safety concerns and appropriate use of the medication. In some cases, absent a REMS, FDA might not have approved a drug for sale because, without the REMS, the drug's risks would have outweighed its benefits.

For brand name prescription drugs, REMS are approved with deadlines by which the drug manufacturer must submit results and an assessment of the effectiveness of the REMS in lessoning the risks associated with the drug. These deadlines are typically 1.5, 3, and 7 years after approval of the REMS. FDA will subsequently review the assessment information provided by the drug manufacturer and determine whether additional information is needed, whether the REMS should be modified, and whether the REMS are meeting the goal of lessening the identified risks of the drug.

FDA first required a product specific REMS for OxyContin in 2010. Recognizing the overuse and addiction potential of all opioid painkillers, in 2012, the FDA approved a post-market shared REMS for a subset of highly potent prescription opioid painkillers known as extended-release (ER) and long-acting (LA) formulations, of which OxyContin is included. In developing the class-wide ER/LA REMS established in 2012, FDA convened an advisory committee that overwhelmingly indicated that the REMS proposed was not sufficient to address the problems associated with use of opioid painkillers.[1]

FDA's review of these REMS is especially important given the ongoing public health crisis arising from the abuse, misuse, addiction, and overdose deaths associated with opioids, and the frequency with which OxyContin is implicated, despite having a REMS in place since 2010. Furthermore, 90 percent of all opioids prescribed are Immediate Release (IR) opioids, which are not currently subject to REMS, despite these opioid drugs being just as addictive and as easily abused as ER/LA formulations.

FDA cannot ensure that the public is protected from the known risks of opioids if it is not consistently requiring REMS for every opioid and if it is not effectively monitoring their performance and responding if they are inadequate. In light of the ongoing opioid-based public health crisis and FDA's role in approving a multitude of these opioid painkillers, I respectfully request that you respond to the following questions no later than May 10, 2016.

1. Please provide me with a copy of FDA's assessment of the success of the drug-specific REMS put in place for OxyContin in 2010.
    a. If FDA did not complete such an assessment, please explain why not.
    b. Did the assessment of the manufacturer of OxyContin (Purdue Pharma) assert that the goals of the REMS were being met?
    c. Did Purdue Pharma provide FDA with complete results and a full assessment of the effectiveness of the REMS according to the specified deadlines? If not, why not, and what was missing from Purdue Pharma's submission?
    d. If the deadlines were not met or the submission was incomplete, did FDA take any action against Purdue Pharma because of its failure to comply?
    e. Did FDA ever request from Purdue Pharma additional information related to the effectiveness of the REMS or an additional assessment to determine whether the REMS should be modified? If, so did Purdue Pharma respond satisfactorily? Please explain.

2. In the last 15 years how many opioid formulations has FDA approved to market? Of these which ones remain approved for market?

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[1] http://www.supportprop.org/wp-content/uploads/2014/12/Minutes_20100722-23-ALSDAC-DSaRM-M1-Minutes.pdf

3. Prior to the statutory establishment of REMS in 2007, FDA utilized Risk Minimization Action Plans (RiskMAPs), viewed as the precursor to the REMS program. Of the opioid drugs approved to market in the last 15 years, how many were subject to RiskMAP or individual drug-specific REMS? Were these REMS or RiskMAP required prior to marketing or as a post-marketing requirement?

4. Of the drugs where REMS were required pre-market, how many of these would have not been approved without the REMS?

5. For each of the opioid drugs that FDA approved in the last 15 years, please provide the following (in instances where a formalized REMS was not yet in place, but a RiskMAP was, please provide information related to the RiskMAP):
    a. FDA's evaluation assessing whether a REMS was needed for that drug, including any reports, emails, letters, memoranda, notes, data, or other related information.
    b. For those drugs where FDA determined a REMS was necessary, FDA's evaluation of the proposed REMS plan, including any reports, emails, letters, memoranda, notes, or other related information.
    c. The final approved REMS plan and any supporting documentation, letters, or related information.
    d. The deadlines required for the drug sponsor to submit results and an assessment of the effectiveness of the REMS.
    e. Any assessment of the approved REMS plan submitted by the drug sponsor to FDA, including both assessments provided in response to deadlines approved with the REMS and assessments or information provided to FDA outside of these required deadlines.
    f. Any proposed or approved changes to the original approved REMS plan submitted by the drug sponsor or initiated by FDA, including proposals or decisions to eliminate the REMS
    g. Documents related to FDA's evaluation of the proposed REMS modification or elimination including any reports, emails, letters, memoranda, notes, data, or other related information.

6. For each of the opioid drugs that FDA approved in the last 15 years **and** where a REMS was required in any form (e.g., drug specific or class; pre-market or post-market) or a RiskMAP was in place, as applicable, please identify:
    a. Which of these drugs met the required deadlines for submission of REMS information?
    b. Which of these REMS were terminated prior to the period determined upon original approval of the REMS?

c. Which of these REMS were extended beyond the period originally intended in the REMS approval?
d. Which of these REMS or RiskMAPs were altered based on evaluations submitted by the sponsor and assessed by the FDA? Please explain the changes that were made and how FDA assessed the need for such alternations.
e. Which of these REMS included **all** the information required by FDA in the FDA assessment plan for the REMS?
f. How many of the REMS met **all** the goals set in the original REMS approval?
g. How many times FDA disagreed with the drug sponsor as to whether the goals of the REMS were met?
h. For drugs that did not meet required deadlines, please provide correspondence between FDA and the drug manufacturer related to the manufacturer's failure to meet the deadlines.

7. Has FDA ever taken an enforcement action against an opioid manufacturer subject to REMS (or RiskMAP, if applicable) because of failure to comply in a timely or complete manner?

8. If a manufacturer does not complete its assessment of the REMS in a manner that provides all the information FDA set forth in its REMS assessment plan, can FDA compel such information from the manufacturer? Would greater statutory authority help the FDA ensure the completeness and quality of information submitted by the manufacturer in its assessments and help FDA determine whether a REMS is effectively mitigating risk?

9. Currently, REMS data is not made public, precluding the ability for independent researchers and stakeholders to evaluate specific REMS activities and effectiveness at mitigating risk. Does FDA have plans to make REMS data more transparent and publically available? If not, why not? If yes, please explain.

10. All ER/LA opioids are subject to class-wide REMS, including abuse-deterrent formulations. In its Opioid Action Plan, FDA recently announced that, as a matter of routine policy, it will not convene advisory panels for abuse deterrent opioid formulations. Does FDA anticipate any policy changes regarding the use of REMS for abuse-deterrent formulations? Please explain.

Thank you for your assistance and cooperation in responding to this request. Should you have any questions, please have your staff contact Dr. Avenel Joseph of my staff at 202-224-2742.

Sincerely,

Edward J. Markey

Edward J. Markey
United States Senator