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ONE HUNDRED SIXTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225–2927
Minority (202) 225–3641

June 25, 2019

Dr. Norman E. Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20903

Dear Acting Commissioner Sharpless:

Pursuant to Rules X and XI of the U.S. House of Representatives, we write to request information from the U.S. Food and Drug Administration (FDA) in response to recent reports concerning two agency actions related to opioids. The FDA actions of interest are: (1) the agency's management of safeguards against high-risk patients being prescribed certain types of fentanyl products made by Insys Therapeutics and other companies that still resulted in inappropriate prescribing according to researchers; and (2) the agency's decision in 2001 that expanded the label for Purdue Pharma's Oxycontin to cover chronic, long-term pain. Last year, the Committee initiated investigations of both Insys and Purdue Pharma. Information from FDA could be pertinent to these oversight interests as well as to continuing interest in FDA's efforts to combat the opioid epidemic.

Report on Inappropriate Fentanyl Prescribing

On February 19, 2019, researchers published an article in the Journal for the American Medical Association entitled, "Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl [TIRF] Products."[1] Fentanyl, which is administered in TIRFs through lollipops, lozenges, or nasal spray, is about 100 times as powerful as morphine. Because of the potency and abuse potential of TIRFs, FDA approved a highly restrictive Risk Evaluation and Mitigation Strategies (REMS) program for all TIRFs to guard against prescribing to patients without opioid tolerance. This REMS program was recently modified by FDA to incorporate additional safety requirements.[2]

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[1] J.E. Rollman, J. Heyward, L. Olson, P. Lurie, J. Sharfstein, G.C. Alexander, *Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products*, Journal of the American Medical Association (Feb. 2019).

[2] U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to strengthen agency's safety requirements aimed at mitigating risks*

Under the REMS program, doctors, pharmacists, and patients receive special instruction on the use of the TIRFs and agree to be part of a small, closed group allowed to prescribe, dispense, and take TIRFs. Before prescribing, dispensing, or using TIRFs, prescribers, pharmacists, and patients are required to certify their understanding of the indications, appropriate use, and risks of TIRFs.[3] Sponsors are required to provide formal assessments of REMS to FDA at six and 12 months, and every 12 months thereafter, from the date of the approval of the REMS modification announced in March 2019.

Based on nearly 5,000 pages of FDA documents from 2012 to 2017 and insurance claims data, the researchers concluded that substantial rates of inappropriate TIRF use occurred under REMS. The researchers looked at the distribution of pharmaceutical fentanyl for cancer patients experiencing "breakthrough pain" despite receiving opioids round the clock. Claims-based data after four years suggested that 12,916 of 25,322 patients who received the TIRFs, or about 51 percent, had not built up tolerance to opioids.[4] A report after 60 months determined that 34.6 to 55.4 percent of patients were ineligible, depending on the product.[5] FDA concluded that its primary goal of keeping the drug out of the hands of ineligible patients was not being met.[6]

The researchers also noted that REMS programs were the subject of a 2013 report by the Department of Health and Human Services (HHS) Office of Inspector General (OIG) generally questioning their overall effectiveness.[7] The OIG issued seven recommendations for FDA to improve the agency's oversight of REMS programs, and FDA agreed with six of these recommendations. However, the researchers found there was little evidence that FDA complied with these recommendations, concluding that "[t]hese findings reinforce many of the concerns noted in the 2013 OIG report."[8]

FDA's Decision to Allow Long-term Use of Oxycontin

On February 24, 2019, the CBS program, *60 Minutes*, explored FDA's decision in 2001 to allow long-term use of Oxycontin despite the lack of research showing it was safe or effective

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associated with transmucosal immediate-release fentanyl products (Mar. 27, 2019) (www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-strengthen-agencys-safety-requirements-aimed).

[3] *See* note 1, at 677.

[4] *Id.* at 680.

[5] *Id.* at 681.

[6] *FDA, drug companies, doctors mishandled use of powerful fentanyl painkiller*, Washington Post (February 19, 2019).

[7] U.S. Department of Health and Human Services, Office of the Inspector General, *FDA Lacks Comprehensive Data to Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety* (Feb. 12, 2013) (OEI-04-11-00510).

[8] *See* note 1 at 683.

for long-term use.[9] Oxycontin was first approved by FDA in 1995 based on scientific evidence that showed it safe and effective when used short-term.[10] However, in 2001, FDA expanded the label for Oxycontin to include long-term chronic pain.[11] FDA provided a written statement which aired during the program, stating in part:

> The FDA has taken aggressive steps to confront the crisis of opioid addiction and we'll continue to pursue new efforts to address this tragedy. This crisis evolved over many years, and many mistakes were made along the way that expanded its toll. This includes prescribing practices that were far too loose for far too long among far too many doctors. While the agency followed the law in approving and regulating opioids, we at the FDA include ourselves among those who should have acted sooner to slow the growth of this tragic epidemic or limit its scope[.][12]

In addition, then-FDA Commissioner Scott Gottlieb reportedly stated, "it's regrettable we didn't do this [research] many years ago,"[13] when he announced FDA would require long-term opioid studies.

Last year, H.R. 6, the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act,[14] provided FDA with the authority to require post-market studies related to long-term efficacy of controlled substances for pain treatment. H.R. 6 also authorized that new information related to reduced effectiveness be included on the label. Previously, FDA could only require safety studies of drugs on the market. Specifically, section 3041 of the SUPPORT Act clarified FDA post-marketing authorities by

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[9] *Did the FDA Ignite the Opioid Epidemic?*, CBS News 60 Minutes (Feb. 24, 2019) (www.cbsnews.com/news/opioid-epidemic-did-the-fda-ignite-the-crisis-60-minutes); *FDA erred on opioids, ex-commissioner tells '60 Minutes,'* Orlando Sentinel (Feb. 21, 2019) ("The FDA never should have allowed Oxycontin and other opioids to be broadly marketed for chronic pain patients, Dr. David Kessler, the agency former commissioner, tells '60 Minutes.' 'There are no studies on the safety or efficacy of opioids for long-term use,' Kessler tells Bill Whitaker. 'The rigorous kind of scientific evidence that the agency should be relying on is not there.'").

[10] U.S. Food and Drug Administration, *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, (www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse) (accessed May 15, 2019).

[11] *Id.*

[12] See note 9.

[13] *FDA takes fresh look at whether opioids are effective for chronic pain*, Washington Post (Feb. 25, 2019) ("On Sunday, the CBS program '60 Minutes' explored the FDA's decision in 2001 to allow long-term use of Oxycontin despite the lack of research showing it was safe and effective. Gottlieb conceded that 'it's regrettable we didn't do this many years ago.'").

[14] SUPPORT for Patients and Communities Act of 2018, Pub. L. No. 115-271.

amending Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act by extending the safety label changes authority to include both safety and new effectiveness information.

On February 25, 2019, FDA announced that it will require drug companies to study whether prescription opioids are effective in quelling chronic pain.[15] The new research is aimed at all immediate, long-acting, and extended-release opioids taken by patients outside of healthcare settings.[16] FDA is also requiring a second study to determine whether opioids can actually cause users to become more sensitive to pain, a condition known as hyperalgesia.[17]

We respectfully request that FDA provide a briefing to Committee staff with appropriate subject matter experts. To ensure a productive briefing, we would appreciate that FDA address the following:

1. What is FDA's assessment of its management of REMS for TIRFs, and what changes, if any, in managing the REMS program for TIRFs would help make the program more effective? Further, what changes, if any, in managing the program would help to prevent possible abuse by sponsors or REMS participants?

2. What is the status of FDA's implementation of the recommendations in the 2013 HHS OIG report? If there is disagreement with a recommendation, or a lack of implementation, please explain why. If actions are being taken to implement a recommendation, please provide details and timeframe.

3. With regard to the 2001 Oxycontin labeling decision, does FDA see any lessons learned either in its original decision, and/or in its course of conduct after the decision?

4. With regard to the 2001 Oxycontin labeling decision, what would FDA do differently in addition to requiring effectiveness research as recently authorized by the SUPPORT Act?

5. Former FDA Commissioner Gottlieb announced in February 2019 that the agency will require drug manufacturers of opioids to conduct studies related to the efficacy and sensitivity of opioid users to pain. When were drug manufacturers notified of the requirement to conduct such studies? Has FDA reviewed the protocols or study designs of the manufacturers to comply with this requirement? If so, how will the studies be designed? When does FDA expect the effectiveness research to be completed?

6. What additional steps is FDA taking to address and curb opioid and fentanyl abuse?

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[15] *See* note 13.

[16] *Id.*

[17] *Id.*

We appreciate your attention to this matter, and if you have any questions, please contact Kevin McAloon of the Majority Committee staff at (202) 225-2927 and Alan Slobodin of the Minority Committee staff at (202) 225-3641.

Sincerely,

Frank Pallone, Jr.
Chairman

Greg Walden
Ranking Member

Anna G. Eshoo
Chairwoman
Subcommittee on Health

Michael C. Burgess, M.D.
Ranking Member
Subcommittee on Health

Diana DeGette
Chair
Subcommittee on Oversight
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Brett Guthrie
Ranking Member
Subcommittee on Oversight
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