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October 11, 2016

The Honorable Robert Califf
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Commissioner Califf:

The nation is in the midst of an opioid abuse epidemic that is now claiming approximately 30,000 lives annually.[1] While prescription painkillers like OxyContin and illicit drugs like heroin and illegally-manufactured fentanyl have fueled the epidemic, there now appears to be a bourgeoning issue with *prescription* fentanyl. I am particularly concerned that off-label prescribing of the fentanyl drug Subsys — driven by the drug manufacturer's aggressive and illegal marketing activities — may be contributing to the problem.

Fentanyl is a synthetic opioid that is up to 100 times more powerful than morphine.[2] In March 2015, the Drug Enforcement Administration (DEA) issued a nationwide alert on fentanyl as a threat to health and public safety.[3] The consequences of illicit fentanyl use are dire. Across the country, fentanyl-related deaths are continuing to rise at alarming rates. According to the Centers for Disease Control and Prevention, of the almost 30,000 drug overdose deaths nationwide in 2014 that involved some type of opioid,[4] the largest increase in the death rate over the previous year — 80 percent — was due to illicitly manufactured fentanyl and synthetic opioid pain relievers.[5] In the state of Massachusetts, 66 percent of the more than 400 confirmed opioid deaths in the first half of 2016 involved fentanyl, up from 57 percent in 2015.[6]

But illicitly-manufactured fentanyl, which is typically trafficked into the United States from countries like China and Mexico, is not the only problem. Fentanyl prescribed by physicians now appears to be contributing to the epidemic. Specifically, the fentanyl drug Subsys — the subject of a recent article in *STAT*, a health and science publication[7] — has

[1] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm
[2] https://www.drugabuse.gov/drugs-abuse/fentanyl
[3] http://www.dea.gov/divisions/hq/2015/hq031815.shtml
[4] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm
[5] *Id.*
[6] https://www.bostonglobe.com/metro/2016/08/03/fentanyl-drives-continuing-rise-opioid-deaths/ymD6jZpMFB4A6z2JA8ImSK/story.html
[7] https://www.statnews.com/2016/09/30/fentanyl-opioid-insys-subsys/

become widely abused, owing to the aggressive and illegal marketing activities of its manufacturer Insys Therapeutics.

In January 2012, the Food and Drug Administration (FDA) approved Subsys "[f]or the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."[8] The FDA warning accompanying the drug states in part: "SUBSYS is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain."[9] Furthermore, in approving Subsys, the FDA determined that the drug required a risk evaluation and mitigation strategy (REMS) "to ensure the benefits of the drug outweigh the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors,"[10] and included Subsys in the Transmucosal Immediate Release Fentanyl (TIRF) REMS that the FDA had instituted in December 2011.[11] In other words, as *STAT* reported: "Subsys is so powerful, and the risk of addiction and overdose so formidable, that the Food and Drug Administration requires doctors to undergo special training before they are allowed to prescribe it. And it has approved Subsys only for cancer patients who suffer intense flares of pain."[12]

But for the most part, Subsys prescriptions and sales have not come in response to the needs of cancer patients. Rather, by far, Subsys is used "off label" — that is, for a use not specifically approved by the FDA. In fact, as *The New York Times* has reported, "just 1 percent of [Subsys] prescriptions are written by oncologists," about half are written by pain specialists, and "a wide range of doctors prescribe[] the rest, including general practice physicians, neurologists and even dentists and podiatrists."[13] As a result, Subsys has proven very profitable for Insys. The year before Subsys — Insys' only drug — went on the market, the company had no reported revenue; last year it reported revenue of $330 million, and a profit of $58.5 million.[14]

Insys has aggressively and illegally pushed this off-label prescribing. Its tactics have included Insys' targeting physicians who do not treat many cancer patients and paying its sales force higher commissions for selling higher doses of the drug.[15] In June 2016, a former district sales manager and a sales representative in New York were arrested in connection with a kickback scheme to increase Subsys prescriptions.[16] In February 2016, a former Insys sales representative in Alabama pled guilty to violating federal kickback laws in connection with a similar scheme.[17] And in September 2016, federal prosecutors in Connecticut charged a former

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[8] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202788Orig1s000Approv.pdf
[9] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202788Orig1s000lbl.pdf
[10] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202788Orig1s000Approv.pdf
[11] *Id.*; http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm
[12] https://www.statnews.com/2016/09/30/fentanyl-opioid-insys-subsys/
[13] http://www.nytimes.com/2014/05/14/business/doubts-raised-about-off-label-use-of-subsys-a-strong-painkiller.html
[14] https://www.statnews.com/2016/09/30/fentanyl-opioid-insys-subsys/
[15] http://www.nytimes.com/2014/05/14/business/doubts-raised-about-off-label-use-of-subsys-a-strong-painkiller.html
[16] https://www.statnews.com/pharmalot/2016/06/11/fentanyl-opioids-bribes-insys/
[17] https://www.statnews.com/pharmalot/2016/02/22/insys-therapeutics-sales-rep-opioid-kickbacks/

Insys district sales manager with giving kickbacks to doctors and nurses to prescribe Subsys.[18] In August 2015, Insys reached a $1.1 million settlement with the Oregon attorney general to resolve allegations that Insys improperly marketed Subsys in Oregon for off-label uses such as non-cancer neck and back pain.[19] Other investigations are ongoing. Insys' most recent Form 10-Q filed with the U.S. Securities and Exchange Commission in August 2016 discloses that it has received Civil Investigative Demands or subpoenas from authorities in Massachusetts, Arizona, Illinois, Florida, and New Hampshire for documents relating to the company's Subsys sales and marketing practices.[20] Insys has also disclosed that it has received a subpoena from the Office of the Inspector General of the U.S. Department of Health and Human Services (HHS) in connection with potential violation of HHS programs.[21]

Insys' improprieties involving the marketing and promotion of Subsys have proven costly to the federal government. Medicare Part D reimbursements for off-label use of Subsys have resulted in the federal government's payment of tens of millions of dollars for questionable Subsys prescriptions that may have also led to the overdose deaths of people who should never have received the drug in the first place. In 2013, Medicare paid $30 million for Subsys prescriptions.[22] Only one year later, in 2014, it paid more than three times that — $97 million.[23]

In April 2016, I wrote you concerning the administration and efficacy of the FDA's REMS programs. In that letter, I stated that the "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 it is not effectively monitoring their performance and responding if they are inadequate."[24] Insys' aggressive and illegal marketing of Subsys points up the need for the FDA to vigorously monitor and enforce its REMS, and I have yet to receive a complete response to my April letter.

Insys' wrongdoing also underscores the need for the FDA to reign in any improper and dangerous marketing and promotion of off-label use. The FDA is currently engaged in a comprehensive review of its regulations and policies governing firms' communications about off-label uses, and will hold a public meeting in November to help inform its policy development in this area.[25] As the FDA considers potential restrictions on off-label marketing and promotion, Insys' aggressive and illegal behavior in pushing Subsys for off-label use should factor heavily in the FDA's decision-making.

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[18] https://www.statnews.com/pharmalot/2016/09/29/insys-manager-arrested-kickback/
[19] http://www.doj.state.or.us/releases/Pages/2015/rel080515.aspx
[20] http://secfilings.nasdaq.com/filingFrameset.asp?FilingID=11527974&RcvdDate=8/5/2016&CoName=INSYS%20THERAPEUTICS%2C%20INC.&FormType=10-Q&View=html
[21] *Id.*
[22] https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/PartD2013.html
[23] https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/PartD2014.html
[24] http://www.markey.senate.gov/imo/media/doc/LTR%20-%20FDA%20-%20REMS%20-%204-19-16.pdf
[25] https://www.federalregister.gov/documents/2016/09/01/2016-21062/manufacturer-communications-regarding-unapproved-uses-of-approved-or-cleared-medical-products-public

The FDA must not become complicit in the growing prescription fentanyl problem this country is combating. Yet improper off-label prescribing of Subsys appears to be contributing to the opioid abuse epidemic. Accordingly, by November 1, 2016, I would appreciate answers to the following questions:

1. How is off-label prescribing of Subsys — for example, for neck and back pain — consistent with the FDA's warning accompanying the drug, which states: "SUBSYS is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain"?

2. How is off-label prescribing of Subsys — for example, for neck and back pain — consistent with the TIRF-REMS, which restricts the use of "TIRF medicines . . . to manage breakthrough pain in adults with cancer who are routinely taking other opioid pain medicines around-the-clock for pain"?[26]

3. Has Insys submitted its required assessment of the TIRF-REMS for Subsys?[27] If so, please provide a copy of Insys' assessment. If not, why not? If Insys has submitted its assessment of the TIRF-REMS, has the FDA completed its review of the assessment?[28] If so, please provide a copy of the FDA's review. If not, why not?

4. Is the FDA taking any steps in response to Insys' pattern of aggressive and illegal off-label marketing of Subsys? If so, what is the FDA doing? If not, why not?

Thank you in advance for your assistance and your cooperation in responding to these requests. Should you have any questions, please contact Andrew Cohen of my staff at 202-224-2742.

Sincerely,

Edward J. Markey

Edward J. Markey
United States Senator

[26] http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm
[27] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202788Orig1s000Approv.pdf
[28] http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf