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

975 JFK FEDERAL BUILDING
15 NEW SUDBURY STREET
BOSTON, MA 02203
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January 13, 2022

The Honorable Janet Woodcock, MD
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

Dear Acting Commissioner Woodcock,

I write to raise concerns about the nomination of Dr. Robert Califf to serve as Commissioner of the Food and Drug Administration (FDA). We continue to live with the consequences of the FDA's failure to effectively regulate opioids. I remain alarmed that the agency has not done enough to account for or reform its processes for reviewing these supercharged painkillers.

Throughout the COVID-19 pandemic, the opioid epidemic has worsened. More than 100,000 Americans died from a drug overdose in the twelve-month period ending in April 2021; more than 75 percent of these deaths involved an opioid, a record level.[1] In Massachusetts, 1,613 people died of opioid-related overdoses in the first nine-months of 2021.[2] But these are only the latest impacts of this crisis. Since the FDA's approval of OxyContin in 1995, the United States has endured a scourge of opioid misuse, overdose, and death. Although the current main driver of the opioid overdose crisis is illicit fentanyl, prescription opioids still serve as a dangerous gateway to opioid use disorder. In 2020, pharmacies in the United States filled 142,816,781 prescriptions for opioid medications, enough for almost half of the entire U.S. population. Unbelievably, this amount still represents a decline from peak opioid prescribing in 2012 when the opioid dispending rate was 81.3 prescriptions per 100 Americans.[3] Stronger regulation of prescription opioids continues to have a role in controlling this epidemic.

[1] Dan Keating & Lenny Bernstein, *100,000 Americans died of drug overdoses in 12 months during the pandemic*, Washington Post (Nov. 17, 2021), https://www.washingtonpost.com/health/2021/11/17/overdose-deaths-pandemic-fentanyl/.
[2] *Data Brief: Opioid-Related Overdose Deaths among Massachusetts Residents*, Massachusetts Department of Public Health (Nov. 2021), https://www.mass.gov/lists/current-opioid-statistics.
[3] *U.S. Opioid Dispensing Rate Map*, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control (Nov. 10, 2021), https://www.cdc.gov/drugoverdose/rxrate-maps/index.html.

The FDA's failure to effectively regulate opioids unquestionably contributed to this crisis. During the past 25 years, the FDA repeatedly rubberstamped new prescription opioids that increased the risk of misuse and dependence and failed to limit the broad availability of these drugs.[4] As evidence of the harm these opioids cause became clear, the FDA acted too slowly to remove them from the market or place restrictions on their labels.[5] Even well into the crisis, the FDA approved powerful new opioids either over the express objections of its advisory committees or without convening an advisory committee at all.[6] And the FDA's use of the authorities for post-market surveillance—e.g. to require reporting of adverse events, education of prescribers, or limitations on use—have failed to mitigate these drugs' harms, and yet again, the FDA has not acted fast enough to improve this post-market surveillance when its failings became evident.[7]

I consistently raised concerns about the FDA's egregious mishandling of opioid approvals when Dr. Califf was first nominated to be Commissioner in 2015. At that time, I opposed Dr. Califf's nomination until the agency took steps to rescind approval for pediatric OxyContin, empanel advisory committees for all opioid regulatory decisions, and consider public health factors in opioid regulatory decisions, in particular the impact of new opioids on opioid misuse and dependence.[8] In response to this strong criticism of the role of the FDA in the opioid crisis, in 2016 Dr. Califf and Dr. Woodcock requested a National Academy of the Sciences (NAS) study of FDA's policies for evaluating opioids,[9] which the NAS completed in 2017.[10] That study emphasized many of the efforts I urged Dr. Califf and the FDA to undertake, in particular the need to include public health factors at every level of FDA regulation of opioid drugs.

However, the FDA has not implemented many of these recommendations and where it has taken steps to do so, it has not gone far enough to require action from manufacturers. For example, in 2019, the FDA issued a draft guidance on risk assessment for opioid analgesic

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[4] Andrew Kolodny, *How FDA Failures Contributed to the Opioid Crisis*, AMA J. of Ethics (Aug. 2020), https://journalofethics.ama-assn.org/article/how-fda-failures-contributed-opioid-crisis/2020-08.

[5] Gerald Posner, *FDA's Janet Woodcock failed to stop the opioid epidemic*, USA Today (Feb. 3, 2021), https://www.usatoday.com/story/opinion/2021/02/03/janet-woodcocks-failure-fda-opioid-epidemic-column/4352787001/.

[6] Senator Ed Markey, Press Release, *Senator Markey Announces Hold on FDA Chief Nominee Citing Concerns With Agency's Failures On Opioid Painkiller Approvals* (Jan. 25, 2016), https://www.markey.senate.gov//news/press-releases/senator-markey-announces-hold-on-fda-chief-nominee-citing-concerns-with-agencys-failures-on-opioid-painkiller-approvals.

[7] Abby Goodnough and Margot Sanger-Katz, *As Tens of Thousands Died, F.D.A. Failed to Police Opioids*, N.Y. Times (Dec. 31, 2019), https://www.nytimes.com/2019/12/30/health/FDA-opioids.html.

[8] Senator Ed Markey, *Press Release, Senator Markey Announces Hold on FDA Chief Nominee Citing Concerns With Agency's Failures On Opioid Painkiller Approvals* (Jan. 25, 2016), https://www.markey.senate.gov//news/press-releases/senator-markey-announces-hold-on-fda-chief-nominee-citing-concerns-with-agencys-failures-on-opioid-painkiller-approvals.

[9] Robert Califf et al., *A Proactive Response to Prescription Opioid Abuse*, New England J. Med. (April 14. 2016), https://www.nejm.org/doi/full/10.1056/NEJMsr1601307.

[10] National Academies of Sciences, Engineering, and Medicine, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* (2017), https://doi.org/10.17226/24781.

drugs.[11] However, this guidance does not explicitly require data on comparative effectiveness and safety of new opioids or discuss consideration of diversion in opioid approvals.[12] Moreover, the FDA has not taken further steps either to improve or finalize this guidance. In the meantime, the FDA has continued to approve new opioids without substantially modifying its processes to account for public health factors, such as the impact of approvals on abuse and diversion.

I met with Dr. Califf in December 2020 to discuss my continuing concerns with the FDA's efforts to regulate opioids. I queried him about the commitments he would make as FDA Commissioner on the NAS study recommendations. I specifically asked about improving the draft guidance on risk analysis of opioid analgesics, as well as his support for mandatory and robust opioid prescriber education through the Opioid Analgesic (OA) Risk Evaluation and Management Strategy (REMS). Additionally, I asked Dr. Califf his views on the role of advisory committees in the FDA's regulatory process, including the role of independent advisory committee decisions that the FDA previously overruled in opioid approvals. During our meeting, Dr. Califf did not commit to the decisive and comprehensive action necessary to ensure reforms that the FDA, under his leadership, would implement on opioid regulation. After years of agency failures and in the midst of a worsening opioid epidemic, we need FDA leadership that is fully committed to using all of the agency's oversight authority to protect public health.

I am, therefore, opposed to Dr. Califf s nomination to be Commissioner of FDA. I am calling on the FDA to commit to action on the following reforms to address the opioid crisis:

1. Undertake a full, comprehensive review of approved opioids, as the 2017 NAS study recommends;
2. Strengthen the draft guidance on including public health factors in risk analysis of opioid analgesics by requiring specific data on the comparative effectiveness and safety of the drug;
3. Finalize this strengthened draft guidance within the next six months, and abstain from approving any new opioid analgesics until this draft guidance is finalized and applied to these drugs; and
4. Enhance post-market surveillance of opioids, including by conducting regular, formal reviews of opioid approvals.

Thank you in advance to your consideration of this matter. Please direct any questions to Adam Axler of my staff at 202-224-2742 or adam_axler@markey.senate.gov.

Sincerely,

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[11] Food and Drug Admin., Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry (draft guidance) (June, 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry.

[12] Sidney Wolfe and Michael Carome, *Comments on the Food and Drug Administration's June 2019 Draft Guidance for Industry Entitled "Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework,"* Public Citizen (Aug. 20, 2019), https://www.citizen.org/article/comments-on-the-fdas-draft-guidance-for-industry-entitled-opioid-analgesic-drugs-considerations-for-benefit-risk-assessment-framework/.

Edward J. Markey
United States Senator

CC: The Honorable Xavier Becerra, Secretary, Department of Health and Human Services