

United States Senate

WASHINGTON, DC 20510

October 31, 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,

We write to express concern about the application pending before the Food and Drug Administration (FDA) for the approval of Dsuvia, a new formulation of the opioid painkiller sufentanil. In the midst of a national opioid overdose crisis, we are particularly alarmed that, on October 12, 2018, the FDA's Anesthetic and Analgesic Drug Product Advisory Committee (AADPAC) proceeded to convene and vote in favor of approving the application — in the absence of the Committee's Chair, who had expressed serious concerns about the product and opposed its approval. We are also deeply troubled that the FDA's full Drug Safety and Risk Management Advisory Committee (DSaRM) was not involved in the approval process. We urge you to deny the application for approval of Dsuvia unless and until you can reconvene both the AADPAC, with its Chair, and the full DSaRM, to ensure more robust and transparent consideration of the safety of what appears to be a very risky opioid product.

Last year, an estimated 29,000 Americans died from an overdose caused by fentanyl or another synthetic opioid, excluding methadone.¹ Although *illicit* fentanyl laced in heroin and other drugs has contributed to this burgeoning number of opioid overdose deaths, the diversion from medically supervised settings of FDA-approved *pharmaceutical* fentanyl and its synthetic analogs such as sufentanil remains a risk that threatens our ability to respond comprehensively to the opioid epidemic.

Sufentanil is 10 times more potent than fentanyl and 1,000 times more powerful than morphine.² Dsuvia's formulation — a small, single tablet administered sublingually — allows for rapid absorption into the blood stream.³ These properties also make the product highly divertible. Sufentanil has been known for decades to be diverted in its current intravenous form, and whether administered intravenously or sublingually, it can deliver a potency that has been known to be lethal in small dosages.⁴ Sufentanil and fentanyl are the two most common substances for

¹ Centers for Disease Control and Prevention National Vital Statistics System, <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm> (last visited Oct. 25, 2018).

² Srihari Tella, Statement before the United States Sentencing Commission for a Public Hearing on Fentanyl and Synthetic Cannabinoids (Dec. 5, 2017), <https://www.uscc.gov/sites/default/files/pdf/amendment-process/public-hearings-and-meetings/20171205/Tella.pdf>.

³ AcelRx Pharmaceutical Products, Dsuvia (last visited Oct. 25, 2018), <http://www.acerx.com/products/dsuvia.php>.

⁴ Letter from Dr. Raeford Brown, Professor of Anesthesiology and Pediatrics at the University of Kentucky College of Medicine and Chair of the AADPAC; Dr. Sidney Wolfe, Founder and Senior Advisor for Public Citizen's Health

which anesthesiologists enter addiction treatment.⁵ Because intravenous sufentanil diversion already occurs, it would be reasonable to assume that a small, tablet form of this potent painkiller — such as Dsuvia — would be an even more easily diverted pathway for someone seeking to access sufentanil outside its intended use.

This diversion risk was born out in the clinical trials for Dsuvia, where some tablets were “dropped,” meaning that they were not successfully administered to the patient.⁴ The FDA recognized this potential for diversion when the manufacturer sought approval for Dsuvia in 2017 and required the company to strengthen its efforts to prevent “use-related errors,” which include dropped tablets.⁶ But experts maintain that the manufacturer’s updated diversion mitigation plan is still insufficient.⁴

Beyond the risk of diversion, we are troubled by the FDA’s advisory committee process for this product. This puzzling and unacceptable course of events is unfortunately reminiscent of previous FDA processes and practices that contributed to the opioid epidemic. Some of us have written letters to your agency and raised concerns with you personally about the FDA’s historical complicity in the nation’s opioid crisis. Some of us have also called on the FDA to convene advisory committees for all new opioid drug application approvals, and have specifically urged the agency to consider addiction, abuse, and dependence in determining if an opioid candidate is safe.⁷ For that reason, we are particularly alarmed that, in considering the application for Dsuvia, the FDA did not convene the full DSaRM.

DSaRM review of a new drug application is intended to ensure that, during the approval process, the potential risks of the drug are discussed and considered. Convening a joint meeting of the full AADPAC and the DSaRM would have signaled that the FDA was fully exploring the relationship between Dsuvia’s risks and benefits. Not empaneling both committees jointly was a missed opportunity to demonstrate that the FDA is committed to fighting the opioid epidemic and that it has learned from past mistakes.

During 2016 and 2017, in all 11 instances where an AADPAC meeting discussed a specific opioid or opioid issues generally, the full DSaRM was invited as a co-committee.⁸ This year, it appears that the FDA has changed this process, to the detriment of public health. The FDA appears to have empaneled, or apparently intends to empanel, AADPAC and DSaRM jointly in

Research Group; Dr. Meena Aladdin, Health Researcher for Public Citizen’s Health Research Group; Dr. Michael Carome, Director for Public Citizen’s Health Research Group to Dr. Scott Gottlieb, FDA Commissioner; Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the FDA; Dr. Sharon Hertz, CDER (Oct. 18, 2018), <https://www.citizen.org/sites/default/files/2451.pdf>.

⁵ Ethan Bryson, MD, and Jeffrey Silverstein, MD, *Addiction and Substance Abuse in Anesthesiology*, *Anesthesiology* (Nov. 2008), <http://anesthesiology.pubs.asahq.org/article.aspx?articleid=1922230>.

⁶ Press Release, AcelRx Pharmaceuticals, AcelRx Pharmaceuticals Receives Complete Response Letter from the FDA for DSUVIA™ NDA (Oct. 12, 2017).

⁷ Press Release, Senator Edward J. Markey, Senator Markey Announces Hold on FDA Chief Nominee Citing Concerns with Agency’s Failures on Opioid Painkiller Approvals (Jan. 25, 2016).

⁸ FDA Anesthetic and Analgesic Drug Products Advisory Committee, <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/default.htm> (last visited Oct. 27, 2018).

just six of the nine instances where an opioid product or general opioid discussion occurred or may occur in 2018.⁸

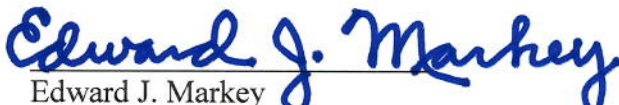
Further adding to the infirmity of the FDA's Dsuvia approval process, the AADPAC Chair was absent the day of the committee vote. It hardly inspires confidence in the approval process when a consequential vote shrouded in controversy proceeds without an advisory committee chair or the voices of the full DSaRM, the committee specifically charged with considering safety and risk concerns.


Finally, the historical ineffectiveness of opioid risk evaluation and mitigation strategies (REMS) and the lack of uniform opioid prescriber education — two important issues some of us have previously raised with you and your agency — causes concern. If the FDA approves Dsuvia and it is successfully diverted, unintended users will face grave risks, and it will be extremely challenging to protect them.


Given the tragic arc of the opioid epidemic, it is imperative that the FDA thoroughly and completely vet any new opioids or formulations of existing opioids through a robust, transparent, and fair process. We do not believe the FDA's process for Dsuvia has remotely met this standard. We therefore urge you to deny the application for this product unless and until there is an opportunity for the Chair of the AADPAC and the full DSaRM to fully consider the Dsuvia application before you take any action.

Thank you for your attention to this important public health issue.

Sincerely,


Edward J. Markey
United States Senator


Claire McCaskill
United States Senator


Joe Manchin III
United States Senator


Richard Blumenthal
United States Senator