

April 28, 2022

The Honorable Robert M. Califf, MD, MACC  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Dear Dr. Califf,

As you step into the role of Commissioner of the Food and Drug Administration (FDA), we urge you to take immediate action to address the opioid epidemic that continues to devastate communities across the country. In 2021 alone, at least 216 Granite Staters lost their lives due to opioid overdoses,<sup>1</sup> and 1,512 Hoosiers lost their lives due to opioid overdoses in Indiana.<sup>2</sup> Many people who die from an overdose first become addicted through a legal prescription for OxyContin or other FDA-approved drugs. Despite this harm, the FDA continues to permit doctors to prescribe these drugs to be sold under misleading and inaccurate labels. Now that you have been confirmed, an urgent priority must be to update the FDA's opioid labeling policies to reflect current public health and safety knowledge.

As I outlined in your nomination hearing, the FDA has endangered the public health by approving flawed opioid labels multiple times. Big Pharma's undue influence has led to the FDA making opioid-labeling decisions that exacerbate the opioid epidemic and contradict public health needs, and the FDA has kept these labels in place despite insufficient evidence of their safety and efficacy. For example, in 2001 the FDA permitted labels that indicate OxyContin for long-term use to treat chronic pain, a decision former FDA Commissioner David Kessler has since described as a mistake and "blank check" for the industry.

FDA now has an opportunity to fix these past errors and strengthen the regulation of opioids in order to save lives. We urge the FDA to pursue the following reforms:

### **Revise the Labeling for the Long-Term Use of Opioids**

Currently, many opioid labels make claims about "daily, around the clock, long-term" efficacy. However, the Centers for Disease Control and Prevention concluded there was "insufficient evidence to determine whether pain relief is sustained and whether function or quality of life improves with long-term opioid therapy."<sup>3</sup> It found "no study of opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for chronic pain [that] evaluated long-term (≥1 year)

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<sup>1</sup> New Hampshire Information and Analysis Center, "New Hampshire Drug Monitoring Initiative," (2021), <https://www.dhhs.nh.gov/dcbcs/bdas/documents/dmi-jan-2022.pdf>.

<sup>2</sup> Indiana Department of Health, "Indiana Drug Overdose Dashboard," (2021), <https://www.in.gov/health/overdose-prevention/data/indiana>.

<sup>3</sup> Deborah Dowell, Tamara Haegerich, and Roger Chou, "CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016," *Morbidity and Mortality Weekly Report*, 65 (2016): 1-49, <https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm>; see also James Heyward et al., "Key Evidence Supporting Prescription Opioids Approved by the U.S. Food and Drug Administration, 1997 to 2018," *Annals of Internal Medicine*, 173 (2020): 956-963.

outcomes related to pain, function, or quality of life.”<sup>4</sup> In February of this year, the Agency for Healthcare Research and Quality conducted a thorough literature review and found zero randomized control trials that evaluate the long-term benefits of opioids versus placebos.<sup>5</sup> In light of both of these government agency findings, we encourage FDA to revise the labeling of opioids by removing unsupported claims about their long-term efficacy.

### **Replace Abuse-Deterrent Language**

FDA currently uses the term “abuse deterrent” in its labeling to convey that an opioid is harder to crush or inject. However, patients and providers often misunderstand the term, mistakenly believing that the drug is less likely to cause addiction.<sup>6</sup> FDA should immediately remove this term from product labels and identify evidence-based language that more accurately conveys the intended meaning.

### **Evaluate the Efficacy of Enriched Enrollment Randomized Withdrawal Trials**

We are also concerned by the ongoing use of enriched enrollment randomized withdrawal (EERW) research designs for clinical trials. Opioid manufacturers have used this research design to artificially inflate the effectiveness of the drug in the clinical trial by removing patients who are not responsive or have adverse effects. This research design limits the generalizability of the trials, underestimating the frequency of adverse effects and overstating the drug’s efficacy.<sup>7</sup> As a result, opioids that were tested on a select group of homogenous individuals are being marketed for everyone. As a group of experts recently recommended in the *Annals of Internal Medicine*, FDA should “stop relying on EERW designs to assess opioid efficacy.”<sup>8</sup>

Physicians and other prescribers rely on the FDA’s label to guide and inform clinical decisions. The label should be based on the best available science, in order for medications to provide the most benefit for patients, with the least harm.

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<sup>4</sup> Deborah Dowell, Tamara Haegerich, and Roger Chou, “CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016,” *Morbidity and Mortality Weekly Report*, 65 (2016): 1-49, <https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm>.

<sup>5</sup> Roger Chou, et al., “Treatments for Chronic Pain. Comparative Effectiveness Review No. 229,” *Agency for Healthcare Research and Quality*, 20-EHC011, (2022), <https://effectivehealthcare.ahrq.gov/products/opioids-chronic-pain/research>.

<sup>6</sup> Catherine S. Hwang, et al., “Primary Care Physicians Knowledge and Attitudes Regarding Prescription Opioid Abuse and Diversion,” *Clinical Journal of Pain*, 32 (2016): 279-284; National Center for Health Research, “NCHR’s Comments on FDA’s Information Collection Activities on Abuse Deterrent Formulations,” (2020), <http://www.center4research.org/nchrs-comments-on-fdas-information-collection-activities-on-abuse-deterrent-formulations>.

<sup>7</sup> Andrea D. Furlan, et al., “A Comparison Between Enriched and Nonenriched Enrollment Randomized Withdrawal Trials of Opioids for Chronic Noncancer Pain,” *Pain Research and Management*, 16 (2011): 337-351; Nathaniel Katz, “Enriched Enrollment Randomized Withdrawal Trial Designs of Analgesics: Focus on Methodology,” *Clinical Journal of Pain*, 25 (2009): 797-807.

<sup>8</sup> James Heyward et al., “Key Evidence Supporting Prescription Opioids Approved by the U.S. Food and Drug Administration, 1997 to 2018,” *Annals of Internal Medicine*, 173 (2020): 956-963.

The Honorable Robert M. Califf, MD, MACC

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Page 3

During your confirmation hearing, you stated, "I am committed to do a comprehensive review of the status of opioids early in my tenure...that would include everything, including the labels." Our constituents expect you to act on this commitment, reduce the harm that opioids can cause to individuals, and restore the public's trust in the FDA.

We look forward to seeing FDA address these issues. Please let us know the FDA's plans and timelines for progress by May 19.

Sincerely,



Maggie Hassan



Mike Braun