

# United States Senate

WASHINGTON, DC 20510

March 27, 2019

The Honorable Scott Gottlieb, M.D.  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993

Dear Commissioner Gottlieb:

We appreciate your focus on the devastating opioid crisis and read with interest the statement you released outlining the FDA's efforts to address the opioid crisis following a recent 60 Minutes report entitled, "Did the FDA Ignite the Opioid Epidemic?"<sup>1</sup> While this statement touched on a number of important steps the FDA is planning for the coming year, such as supporting the development of new medication-assisted treatment, advancing research in non-addictive pain treatments, and strengthening drug interdiction efforts, it failed to address a number of critical questions.

You have said that the FDA made mistakes regarding the opioid crisis and have pledged to learn from these mistakes.<sup>2</sup> The FDA must provide a fuller accounting of its past decision-making processes for the approval and labeling of opioid drugs, including the influence that pharmaceutical executives had on these decisions. While some of these issues concern decisions and actions that the FDA took decades ago, getting answers to these questions is vital to ensure that current opioid labels protect public health and safety, and to prevent the FDA from repeating its past mistakes in the approval of new opioid products.

Throughout your tenure as FDA Commissioner, you have spoken repeatedly about the gravity of the opioid crisis, and we respectfully request that you answer the following questions in writing before your time at the agency concludes.

1. You referred to "past mistakes" in the statement you issued after the 60 Minutes report.<sup>3</sup> Specifically:
  - a. What are the past mistakes you were referring to?
  - b. When were these mistakes made?
  - c. For each past mistake identified, what actions has FDA taken in response?

---

<sup>1</sup> Bill Whitaker, "Did the FDA Ignite the Opioid Epidemic?" in 60 Minutes, CBS News, February 24, 2019.

<sup>2</sup> U.S. Food & Drug Administration, U.S. Department of Health and Human Services, "Statement from FDA Commissioner Scott Gottlieb, M.D. on the Agency's 2019 Policy and Regulatory Agenda for Continued Action to Forcefully Address the Tragic Epidemic of Opioid Abuse," news release, February 26, 2019.

<sup>3</sup> Ibid.

2. Has the FDA conducted a review – either formal or informal – of the process surrounding its original 1995 approval of the OxyContin label and the 2001 change to the OxyContin label?
  - a. If so, did such review find that the FDA followed all relevant rules and regulations?
  - b. Specifically, did such review find that the required efficacy trials were conducted and that data from such trials was provided to the FDA for OxyContin at the 10mg, 20mg, 40mg, 80mg, and 160mg doses?
  - c. If efficacy trials for each dose were not performed, why not?
3. Since the 1995 approval of OxyContin, how many adverse events reports involving deaths has FDA received?
  - a. How many adverse event reports involving deaths were received by FDA for individuals younger than 21 years old?
4. Did FDA require efficacy trials for its approval of Roxicodone 15mg and 30mg oxycodone tablets in 2000? If not, why were efficacy trials not required?
5. In the FDA Briefing Document for the Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee & Drug Safety and Risk Management Advisory Committee held on June 26, 2018, FDA indicated that the safety and efficacy of oxycodone ER was based on bioequivalence to immediate release Roxicodone.<sup>4</sup> On what basis did FDA come to the conclusion that extended release and immediate release oxycodone are bioequivalent?
  - a. If studies demonstrating safety and efficacy of Roxicodone were not performed, is it appropriate for FDA to assume that a drug bioequivalent to Roxicodone is safe and effective?
6. In the years since 2001, has the FDA at any time formally or informally considered removing chronic pain from the label of opioid products? Have any offices at FDA or any staff involved in the review of opioid products at the FDA ever recommended removing chronic pain from the label of opioid products?
7. The CDC,<sup>5</sup> DOD/VA,<sup>6</sup> and American Academy of Neurology<sup>7</sup> have said that the risks of opioid therapy for chronic conditions such as headache, fibromyalgia, and chronic low back pain likely outweigh the benefits.
  - a. Does the FDA agree with this assessment?
  - b. If so, has the FDA taken any action as a result?
  - c. Is any additional action being considered?

---

<sup>4</sup>U.S. Food and Drug Administration, Office of Drug Evaluation II, Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee, by Sharon Hertz.

<sup>5</sup> Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016. MMWR Recomm Rep 2016;65 (No. RR-1):1–49.

<sup>6</sup> “We recommend against initiation of long-term opioid therapy for chronic pain. (Strong against)” Department of Veteran Affairs, Department of Defense, VA/DoD CLINICAL PRACTICE GUIDELINE FOR OPIOID THERAPY FOR CHRONIC PAIN (2017).

<sup>7</sup> G. M. Franklin, “Opioids for Chronic Noncancer Pain: A Position Paper of the American Academy of Neurology,” *Neurology* 83, no. 14 (2014).

8. The CDC<sup>8</sup> and VA/DoD<sup>9</sup> have warned against prescribing opioids at doses that exceed 90mg morphine equivalents per day.
  - a. Does the FDA agree with this assessment?
  - b. If so, has the FDA taken any action as a result?
  - c. Has the FDA contemplated any labeling changes that would reflect this warning?
  - d. Is any other action being considered?
  
9. At the request of the FDA, the National Academies of Sciences, Engineering, and Medicine in 2017 released its Strategies for Reducing the Opioid Epidemic, which included a new framework for considering the approval and removal of opioid products that takes into account the public health impact.<sup>10</sup> You said that you would be implementing this framework.<sup>11</sup>
  - a. What specific steps has the FDA taken to implement this framework?
  - b. Has the FDA considered using the framework to seek removal of opioid products from the market, other than Opana?
  
10. Last month, you said that the FDA will require drug companies to initiate studies on whether prescription opioids are effective for treating chronic pain.<sup>12</sup> The FDA has already repeatedly claimed that it would require post-market studies, including in 2013, when the FDA said it would require studies on the safety of opioids for treating chronic pain.<sup>13</sup> What is the status of these post-market studies?
  
11. When the FDA called for post-market studies in 2013, Director of the Center for Drug Evaluation and Research Janet Woodcock wrote, that “FDA is not aware of adequate and well-controlled studies of opioid use longer than 12 weeks” and that the FDA was thus exercising its authority to require “opioid drug sponsors to conduct PMRs to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of opioid analgesics.”<sup>14</sup> Title 21, Sec. 314.126 of the Code of Federal Regulations states “adequate and well-controlled investigations provide the primary basis for determining if there is ‘substantial evidence’ to support the claims of effectiveness.” What is the legal justification for the FDA’s current label for extended-release opioids if the agency acknowledged in 2013 that such “adequate and well-controlled” studies did not exist?

---

<sup>8</sup> Department of Health and Human Services, Centers for Disease Control and Prevention (U.S.), Factsheet CDC Guideline for Prescribing Opioids for Chronic Pain.

<sup>9</sup> Department of Veteran Affairs, Department of Defense, VA/DoD CLINICAL PRACTICE GUIDELINE FOR OPIOID THERAPY FOR CHRONIC PAIN (2017).

<sup>10</sup> “Strategies for Federal Agencies: Confronting Pain Management and the Opioid Epidemic,” The National Academies of Sciences, Engineering, and Medicine, July 13, 2017.

<sup>11</sup> U.S. Food & Drug Administration, U.S. Department of Health and Human Services, “Statement from FDA Commissioner Scott Gottlieb, M.D. on agency’s approval of Dsuvia and the FDA’s future consideration of new opioids” news release, November 2, 2018.

<sup>12</sup> Lenny Bernstein and Laurie McGinley, “FDA Takes Fresh Look at Whether Opioids Are Effective for Chronic Pain,” Washington Post, February 25, 2019.

<sup>13</sup> “Docket No. FDA-2012-P-0818,” Janet Woodcock, MD, Director of Center for Drug Evaluation and Research to Andrew Kolodny, MD, President, Physicians for Responsible Opioid Prescribing September 10, 2013.

<sup>14</sup> Ibid.

12. The enriched enrollment randomized withdrawal (EERW) study design for opioid analgesics is a clinical trial methodology that limits inclusion to patients who tolerate opioids and are likely to be physiologically dependent on opioids after taking them in an open-label phase. Critics have called this methodology scientifically unsound and have said that it amounts to cooking the books.<sup>15</sup>
- a. In 2013, the Washington Post reported on a group known as IMMPACT, which held meetings that pharmaceutical companies paid tens of thousands of dollars to participate in and advised the FDA on clinical trials.<sup>16</sup> In a presentation entitled, "The Impact of IMMPACT," former chief of the FDA's analgesic division Bob Rappaport touted "A New Successful Trial Design" that resulted from the IMMPACT meetings.<sup>17</sup> Was the "new successful trial design" that emerged from the IMMPACT meetings EERW?
  - b. Have any offices at FDA or any staff involved in the review of opioid products at the FDA ever raised concerns about the EERW study design?
  - c. Has FDA ever convened an advisory committee meeting to discuss and vote on the appropriateness of using EERW?
  - d. Opioid dependent pain patients switched to placebo are likely to experience withdrawal symptoms. How are double-blind requirements maintained when patients are switched from a drug with a noticeable psychoactive effect to placebo and when withdrawal symptoms are experienced?
  - e. If increased pain sensitivity and worsening of pain are common during opioid withdrawal, is it fair to assume that opioid dependent patients switched to placebo in an EERW study will have an increase in pain?
  - f. In light of these concerns, will FDA consider convening an advisory committee meeting to review and vote on the appropriateness of EERW designed for opioid approvals?

Thank you in advance for your timely response.

Sincerely,



MARGARET WOOD HASSAN  
United States Senator



EDWARD J. MARKEY  
United States Senator

<sup>15</sup> Jonah Campbell and Nicholas B. King, "[Unsettling Circularity](#)": Clinical Trial Enrichment and the Evidentiary Politics of Chronic Pain," *BioSocieties* 12, no. 2 (2017): doi:10.1057/biosoc.2016.7.

<sup>16</sup> Peter Whoriskey, "[Pharmaceutical Firms Paid to Attend Meetings of Panel That Advises FDA, E-mails Show](#)," *Washington Post*, October 6, 2013.

<sup>17</sup> Bob A. Rappaport, MD, "[The Impact of IMMPACT](#)" (presentation, Washington, DC, March 9, 2007).