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December 21, 2015

The Honorable Sylvia Mathews Burwell
Secretary
United States Department of Health & Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Burwell,

Thank you for talking with me on December 18th about my concerns with the Food and Drug Administration's (FDA's) decision-making related to prescription opioid painkillers. As you know, the country is in the midst of a prescription opioid and related heroin epidemic that is claiming lives at an alarming rate. According to the Centers for Disease Control and Prevention (CDC), in 2014, opioids were involved in 28,647 deaths or 61% of all overdose deaths in this country.[1] In 2014 alone, my state of Massachusetts lost more than 1,200 people to opioid overdose deaths, a figure that is tragically expected to be even higher for 2015.[2] I am therefore especially troubled by the FDA's recent handling of the process by which it approved a new pediatric indication for the prescription painkiller OxyContin — a process that reflects a continuing disregard for public safety when it comes to prescription opioids. This letter is intended to expand upon our discussion and provide you with more context for my concerns.

On December 7, 2012, an FDA advisory committee empaneled to consider the application for approval of the extended release prescription opioid Zohydro voted 11-2 against the drug's approval. Those committee members, who voted no, did so in reflection of the serious public safety concerns raised by the entire

[1] Rudd, R., et al. Increases in Drug and Opioid Overdose Deaths—United States, 2000-2014. Centers for Disease Control and Prevention: Morbidity and Mortality Weekly Report. December 18, 2015

[2] https://www.bostonglobe.com/metro/2015/10/21/new-data-shows-opioid-overdose-epidemic-continuing/BpblfS1nPPwXMCj9NW4FgP/story.html.

category of FDA-approved opioid painkillers. As advisory committee member Dr. James Ware of Harvard University's T.H. Chan School of Public Health put it, "the entire class is problematic in terms of abuse and safety issues," and he emphasized that his "negative vote was not about the drug [Zohydro] per se, but it was about the class."[3] Despite the misgivings of eleven expert advisory committee members, like Dr. Ware, on October 25, 2013, the FDA approved Zohydro to be marketed and sold in the United States, without having addressed the problematic addiction, abuse, and safety issues.

Almost two years later on August 14, 2015, the FDA approved a new pediatric indication for OxyContin — for children aged 6 to 11 — without even empaneling an advisory committee.[4] The FDA did not convene an advisory committee despite FDA's own guidance document, which calls for empaneling such a committee when the matter is of significant public interest, highly controversial, or requires a special type of expertise.[5] Under that same FDA guidance document, a question of "pediatric dosing" is given as an example of when one of those factors, triggering an advisory committee, is often met.[6] Therefore, under the FDA's own guidance document, and especially in light of the concerns voiced by the Zohydro advisory committee members about other drugs in the opioid painkiller class including OxyContin, being highly addictive and a threat to public safety, the FDA should have empaneled an advisory committee on the pediatric OxyContin question.

In the past three years, while the use and abuse of prescription-opioids and heroin has surged across the country and is responsible for a skyrocketing number of deaths, the FDA has overruled one advisory committee that voted overwhelmingly against approving a new opioid, and bypassed altogether the empaneling of an advisory committee on the question of a new use for another opioid. Indeed, on the pediatric OxyContin question, the FDA appears to have willfully blinded itself to expert advice on a serious opioid-safety question and improperly shortcut the regulatory process in order to avoid another overwhelmingly negative vote on an opioid-approval question.

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[3] FDA Center for Drug Evaluation and Research, Anesthetic and Analgesic Drug Products, Advisory Committee, Hr'g Tr. 383:1-15 (Dec. 7, 2013) [hereinafter "FDA Hr'g Tr."], *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM339619.pdf.

[4] http://www.fda.gov/Drugs/NewsEvents/ucm456973.htm.

[5] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125651.pdf at 4.

[6] *Id.* at 5.

On November 18, 2015, I met with Dr. Robert Califf, who has been nominated as the next FDA Commissioner. I raised with him these and other concerns about the FDA's handling of prescription opioid questions. Unfortunately, Dr. Califf did not give me confidence that under his stewardship the FDA would confront the highly problematic manner in which the agency is approaching these issues.

I am therefore inclined to place a hold on Dr. Califf's nomination unless the FDA commits to me that it will do the following:

(1) rescind the pediatric OxyContin approval and empanel an advisory committee to reconsider the question, as it should have in the first instance;

(2) agree to empanel advisory committees on any future opioid-approval questions and require such committees considering opioid-approval questions to expressly consider the issues of addiction, abuse, and dependence, not just dosing-related information, in the context of determining whether the drug is safe; and

(3) immediately ensure that the issues of addiction, abuse, and dependence are criteria considered by the FDA when making an ultimate decision about a prescription opioid approval or indication.

Please direct any questions about this request to Avenel Joseph and Andrew Cohen of my staff at 202-224-2742 or Avenel_Joseph@markey.senate.gov and Andrew_Cohen@markey.senate.gov.

Sincerely,

Edward J. Markey

Edward J. Markey
United States Senator