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October 18, 2018

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Commissioner of Food and Drugs
Food and Drug Administration
10903 New Hampshire Avenue
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Janet Woodcock, M.D.
Director
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Sharon Hertz, M.D.
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Office of Drug Evaluation II, Office of New Drugs
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Dear Drs. Gottlieb, Woodcock, and Hertz:

Public Citizen, a nonprofit consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) to reject AcelRx Pharmaceuticals' new drug application (NDA) for the sublingual dosage form of the high-potency opioid sufentanil, stated by the Drug Enforcement Agency to be 1,000 times more potent than morphine,¹ despite the 10 to 3 vote on October 12, 2018, by FDA's Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) favoring such approval. As you know, the current deadline for your decision is November 3, 2018.

Our reasons for urging the FDA not to approve sublingual sufentanil tablets include the following:

- (1) A strong statement opposing approval from the FDA's AADPAC's long-standing Chair, Dr. Raeford Brown, who is a cosigner of this letter. Dr. Brown had previous

¹ Tella SR. Statement before the United States Sentencing Commission for a public hearing on fentanyl and synthetic cannabinoids. December 5, 2017. <https://www.uscc.gov/sites/default/files/pdf/amendment-process/public-hearings-and-meetings/20171205/Tella.pdf>. Accessed October 17, 2018.

commitments and was therefore unable to attend the AADPAC October 12, 2018, meeting, but summarized the basis of his opposition to the approval of sufentanil below.

- (2) The inexplicable failure of the FDA to have the full Drug Safety and Risk Management Advisory Committee (DSRMAC) participate in the October 12, 2018, AADPAC meeting, thereby predictably increasing the odds of a vote favoring FDA approval.
- (3) The FDA's unrealistic and dangerous decision before the meeting — reflected in its AADPAC's briefing materials — that the two major safety problems causing the agency to reject sublingual sufentanil tablets in 2017 were no longer a barrier to its approval and that the benefits thereby outweigh the risks.

The following is a more detailed discussion of each of these reasons.

Dr. Brown's statement opposing approval

As the Chair of the FDA advisory committee charged with evaluation of analgesic products, I have been involved in the assessment of countless opioid products over the last four years. During that time, I have developed a sensitivity to the harms that can be associated with the marketing of new opioid compounds and have been forced to consider the lack of ability of the agency to predict the behavior of opioid drugs and to enforce post-marketing regulation. It is my observation that once the FDA approves an opioid compound, there are no safeguards as to the population that will be exposed, the post-marketing analysis of prescribing behavior, or the ongoing analysis of the risks of the drug to the general population relative to its benefit to the public health. Briefly stated, for all of the opioids that have been marketed in the last 10 years, there has not been sufficient demonstration of safety, nor has there been post-marketing assessment of who is taking the drug, how often prescribing is inappropriate, and whether there was ever a reason to risk the health of the general population by having one more opioid on the market.

Sufentanil is a case in point. It has been used as an intravenous (IV) agent by clinicians only in hospital settings for more than twenty years. It is a very potent opioid with substantial risks of respiratory depression, diversion, abuse, and death. It is so potent that abusers of this intravenous formulation often die when they inject the first dose; I have witnessed this in resuscitating physicians, medical students, technicians, and other health care providers, some successfully, as a part of my duties as a clinician in a major academic medical center. Because it is so potent, the dosing volume, whether in the IV formulation or the sublingual form, can be quite small. It is thus an extremely divertible drug, and I predict that we will encounter diversion, abuse, and death within the early months of its availability on the market.

The agency feels that there is a capability, so far not demonstrated, to regulate this drug so that it is used only in closely controlled settings. In order to have this happen, the education of all prescribers would need to be guaranteed. This has not been demonstrated with any other opioid and, given the lack of teeth in the current risk evaluation and mitigation strategies for opioids,

there is currently no educational nor regulatory scheme that will guarantee that this drug will be used only as described in the label.

Lack of historical ability of the FDA to enforce controls, the pharmacologic potency of the drug, and the ease with which this drug will be diverted are some of the reasons that I would never consider this product for marketing in the U.S. Sublingual sufentanil represents a danger to the general public health and will make our job of protecting Americans more difficult.

The inexplicable failure of the FDA to have the full DSRMAC participate in the October 12, 2018, AADPAC meeting

One reason that the FDA established the relatively new DSRMAC, which first met in 2002,² was to augment the clinical expertise of the relevant clinicians (in the case of the AADPAC, anesthesiologists) with people who had more expertise in drug safety, pharmacoepidemiology, risk management, and other areas, thus increasing the overall effectiveness of advisory committees' reviews of drug safety. One of us (Dr. Sidney Wolfe) was a member of this committee from 2008 to 2012. It is clear from attending the DSRMAC meetings as a member, including many meetings concerning opioids, and from reading transcripts of the meetings that the issues regarding safety were much more definitively discussed than at earlier meetings, prior to the important addition of the DSRMAC. In addition to the nature of the discussions, when votes were taken on the issue of approval of new drugs or the withdrawal of already approved drugs, the views expressed by DSRMAC members had an important influence on the outcome of the votes.

At the October 12, 2018, AADPAC meeting at which the NDA for sublingual sufentanil tablets was considered, all four of the anesthesiologists on the committee, as well as two other anesthesiologists who were temporary voting members, voted to approve the drug. The three votes against approval of sublingual sufentanil tablets were cast by one invited member of DSRMAC (only two DSRMAC members were invited to participate as temporary voting members) as well as a critical care nurse and an epidemiologist/physician, both of whom were temporary voting members. It is likely, if not certain, that had the full DSRMAC attended the meeting, either the drug would have been rejected or the vote would have been much closer, making the FDA's decision to reject it, as we are asking now, less complicated. The FDA appears to have made a deliberate decision to avoid including the full DSRMAC in the review of sublingual sufentanil tablets in order to tilt to outcome of the AADPAC in favor of approval.

Given that there is an ongoing epidemic of preventable prescription-opioid-induced deaths, it is inexcusable and unacceptable that all FDA advisory committee meetings involving opioids do

² Food and Drug Administration. Transcript of the Drug Safety and Risk Management Advisory Committee, July 17, 2002. https://wayback.archive-it.org/7993/20170404085504/http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3874T1_01.pdf. Accessed October 17, 2018.

not include the full DSRMAC, a serious mistake made in the case of sublingual sufentanil tablets.

FDA’s unwarranted decision to reverse its assessment of the safety problems regarding sublingual sufentanil tablets based on inadequate evidence

In addition to accepting as adequate the increased number of patients given the 30-microgram dose of sublingual sufentanil tablets in clinical trials since the 2017 rejection of sufentanil, the FDA wrongly bought into the company’s proposal to add an additional safeguard to avoid the “dropped doses,” instances in which the researchers could not account for all of the sufentanil dose units. This was correctly considered during the review of the initial NDA submission to be a possible route for diversion or misuse.

This logic misses well-documented instances of diversion not mentioned in the briefing documents: Diversion of sufentanil by anesthesiologists and other medical personnel, mentioned in Dr. Brown’s statement above. This is discussed in two published studies. The first, entitled *Evidence of Addiction by Anesthesiologists as Documented by Hair Analysis*, stated that:

Numerous factors have been proposed to explain the high incidence of abuse among anesthesiologists. They have easy access to a wide range of potent psychoactive drugs. Opioids promote rapid tolerance and dependence, particularly the highly lipid soluble agents (e.g. fentanyl). Diversion of these agents is relatively simple since only small doses will initially provide an effect desired by the abuser. Traditionally, opioids are the drugs of choice selected for abuse by anesthesiologists. Fentanyl and sufentanil are the most common, followed by meperidine and morphine.³

The second article, entitled *Anesthetic Drug Abuse by Anesthesiologists*, states that:

Despite the fact that alcohol abuse is the most common among anesthesiologists, the abuse of anesthetic agents causes more concern, due to its high dependence potential and consequences, which are often fatal. The most widely used drugs are opioids (fentanyl and sufentanil), propofol and inhalational anesthetics. Young professionals are the most affected. Among the consequences of drug abuse are workplace absence and even death.⁴

In closing, for the above reasons, all of us strongly urge you to reject this needless and dangerous addition to the FDA-approved opioid armamentarium. It has no truly unique benefits and will only add to the worsening, not the mitigation, of the opioid epidemic in this country.

³ Kintz P, Villain M, Dumestre V, Cirimele V. Evidence of addiction by anesthesiologists as documented by hair analysis. *Forensic Sci Int.* 2005;153(1):81-84.

⁴ Jungerman FS, Palhares-Alves HN, Carmona MJ, et al. Anesthetic drug abuse by anesthesiologists. *Rev Bras Anesthesiol.* 2012;62(3):375-386.

Thank you for your prompt attention to this urgent public health matter.

Sincerely,

/s/

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