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December 11, 2018

Scott Gottlieb, M.D.
Commissioner of Food and Drugs
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Your November 2, 2018, public statement on the FDA's approval of Dsuvia

Dear Dr. Gottlieb:

For eight of the last 11 years, one of us has either been a member of the Food and Drug Administration's (FDA's) Drug Safety and Risk Management Advisory Committee (SW, 2008-2012) or a member or Chairperson of the agency's Anesthetic and Analgesic Drug Products Advisory Committee (RB, 2015-present). Based on our involvement in dozens of advisory committee meetings related to the consideration of possible approval of individual opioids and discussions of critical overarching issues concerning opioids with experts within and outside of the agency, it is clear to us that dangerous FDA deficiencies in the regulation of opioids have amplified the devastating effects of these medications on public health.

Many of these long-standing deficiencies were made alarmingly apparent during the FDA's recent review and approval process for AcelRx Pharmaceuticals' new drug application for Dsuvia (sufentanil sublingual tablets) and by your many unsubstantiated and disingenuous comments attempting to justify this approval and other FDA actions related to opioids that were included in your November 2 public statement accompanying the agency's announcement of the approval.¹ We are writing now to provide evidence refuting many of the claims made in your Dsuvia justification statement.

In your statement, you raised two important, but essentially rhetorical, questions, the obvious answers to which should have resulted in an evidence-based FDA decision to reject Dsuvia. You wondered "why do we need an oral formulation of sufentanil?" and "whether or not America needs another powerful opioid while in the throes of a massive crisis of addiction?" Given the evidence of known harms, including diversion and sometimes fatal abuse of the older

¹ Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on agency's approval of Dsuvia and the FDA's future consideration of new opioids. November 2, 2018.

<https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624968.htm>. Accessed December 10, 2018.

intravenous form of sufentanil by anesthesiologists,² you clearly needed to establish, and did allege, unique patient benefits in a futile attempt to create the illusion of a patient-favorable harm-to-benefit profile for the newer sublingual form of the drug, Dsuvia.

One “unique feature” you identified is that “the drug is delivered in a stable [tiny pill] form that makes it ideally suited for certain special circumstances where patients may not be able to swallow oral medication, and where access to intravenous pain relief is not possible. This includes potential uses on the battlefield... [Dsuvia] was a priority medical product for the Pentagon because it fills a specific and important, but limited, unmet medical need in treating our nation’s soldiers on the battlefield.” Revealingly, on the same day Dsuvia was approved, the FDA announced that it had executed a Memorandum of Understanding with the Department of Defense that is intended to expedite the review of medical products intended for military personnel, particularly those products used to treat injuries in battlefield settings.³

The evidence against this example of purported “uniqueness” includes the fact that use of Dsuvia in the setting of severe trauma-induced pain and shock, as encountered in the battlefield, has never been studied. Instead, Dsuvia was tested in clinical trials in patients who had undergone minor surgical procedures such as bunion removal and hernia repair or abdominal laparoscopy. Dsuvia required a median time of nearly an hour to meet the standard of clinically meaningful pain relief for these patients,⁴ indicating that it certainly would not meet the needs of seriously injured soldiers. No competent medic would use an under-the-tongue analgesic that takes an hour to achieve meaningful pain relief because they can, instead, quickly insert an intravenous line and achieve pain relief in minutes using older opioids.

Other purportedly “unique” features you cited include that “Dsuvia is to be reserved for use in patients for whom alternative pain treatment options have not been tolerated, or are not expected to be tolerated, where existing treatment options have not provided adequate analgesia, or where these alternatives are not expected to provide adequate analgesia.” However, in none of the clinical trial settings in which the drug was studied before approval — patients undergoing minor elective surgery and patients in the emergency room — was there evidence that *any* of these implicitly “unique” conditions apply.

To allege risk minimization of this dangerous opioid, you further asserted that “there are very tight restrictions being placed on the distribution and use of this product” and that Dsuvia “will only be made available for use in a certified medically-supervised health care setting, including its use on the battlefield.”

² 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.

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

³ Food and Drug Administration. FDA and DoD formalize collaboration to advance medical products in support of American military personnel. November 2, 2018. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624970.htm>. Accessed December 11, 2018.

⁴ FDA-approved label for Dsuvia: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209128s000lbl.pdf. Accessed December 10, 2018. Pages 22-23.

Dr. Gottlieb, let us be very clear: the FDA has demonstrated no circumstance in which any opioid is approved but not diverted and misused. We have worked with the FDA for years to evaluate evidence that such restrictions and educational processes might prevent inappropriate use and have failed to identify any measures that have been successful. It stands as historical fact that once an opioid is approved, it will inevitably be used for unapproved purposes, diverted, and abused.

As evidence, consider the substance of the August 3, 2018, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee in August of this year. The committees discussed the Risk Evaluation and Mitigation Strategy for transmucosal immediate-release fentanyl products, which are approved for only one purpose: the treatment of severe pain in cancer patients. During this meeting, clear evidence showed that 69 percent of the patients being treated with this drug were not cancer patients,⁵ but patients with other painful conditions, many for which the need for *any* opioid has been called to question. At this juncture, there is no evidence that the FDA or any other group has been able to control misuse, diversion, or abuse of opioids once they are approved.

You stated that a critical question to be addressed in the Dsuvia decision is “Why do we need an oral formulation of sufentanil?” Why indeed? When the FDA continues to approve multiple dosage formulations of opioids such as Dsuvia — in the face of a known public health opioid crisis — it sends a message to the American public that it has no control of the regulatory landscape and, worse, is pandering to the pharmaceutical industry.

In the last eight years, the FDA has encouraged manufacturers to produce unique forms of opioids (so-called abuse-deterrent formulations [ADFs]) that have not demonstrably reduced deaths but have effectively extended the patent life of brand-name opioids. A change in the dynamic of ADF opioid use by abusers, as evidenced by increased intravenous abuse with ADF Opana ER (extended-release oxycodone), led to an outbreak of HIV infections and the ban of Opana ER because it was actually more dangerous than the non-ADF form of the drug. In your November 2 statement, you and your agency took credit for removing Opana ER from the market (“we’ve taken strong actions where appropriate, such as requesting the withdrawal of reformulated [ADF] Opana ER from the market”) but somehow failed to admit that before its approval in 2012, the FDA had already determined that the drug might increase the potential for intravenous abuse and approved it anyway.⁶

You also stated that the following question needs to be addressed: “As we look at the public health implications of each new approval, we should evaluate whether we need to take additional steps to systematically consider new opioids relative to the comparative benefit and risks of other

⁵ Food and Drug Administration. PowerPoint slides for the August 3, 2018, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM616802.pdf>. Accessed December 10, 2018. PDF page 63.

⁶ Public Citizen. Testimony of Sidney Wolfe before the FDA Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees. March 14, 2017. <https://www.citizen.org/sites/default/files/2365.pdf>. Accessed December 10, 2018.

opioids already on the market.” This question has previously been asked and answered. For the last five years, members of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee have strongly suggested that any new opioid products should be considered in light of the products that are already available.

In fact, the July 2017 report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*, issued by a committee of the National Academies of Sciences, Engineering and Medicine (National Academies), validated these comments of the FDA’s advisory committees in strong language, in addition to making other important suggestions for improving FDA opioid regulation.⁷

The National Academies committee was established at the request of your predecessor, Dr. Robert Califf, to study the causes and consequences of the opioid crisis and to recommend actions that the FDA should take to contain it and prevent future recurrences⁸. The National Academies’ report — specifically its recommended framework for approval and monitoring of opioids — has had strong support from the scientific community. Why has the agency not taken definitive drug-specific action based on these recommendations?

Not surprisingly, the National Academies expert committee, after a comprehensive review of the FDA and its role in the regulation of opioids, made the following recommendations for improving the opioid approval process, which should have been put in place prior to the approval of Dsuvia:

1. **Recommendation 6-1: Incorporate public health considerations into opioid-related regulatory decisions** – This recommendation urged the FDA to consider the effects on the overall market for opioids, benefits and risks to the patient and their family, risks associated with diversion, and risks to specific subpopulations or geographic areas that may present distinct risk profiles.
2. **Recommendation 4-1. Consider potential effects on illicit markets of policies and programs for prescription opioids**
3. **Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations**
4. **Recommendation 6-3. Ensure that public health considerations are adequately incorporated into clinical development** – This includes satisfactory clinical trial design. In implementing this recommendation, the FDA should rarely, if ever, use expedited

⁷ Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use. National Academies of Science, Engineering and Medicine. July 13, 2017. <http://nap.edu/24781>. Accessed December 10, 2018.

⁸ Califf RM, J Woodcock, S Ostroff. A proactive response to prescription opioid abuse. *New Engl J Med*. 2016;374(15):1480-1485.

development or review pathways or designations for opioid drugs and should review each application in its entirety.

- 5. Recommendation 6-4. Increase the transparency of regulatory decisions for opioids in light of the committee’s proposed systems approach** – Increasing FDA transparency regarding its regulatory decisions for opioids is critically important. With the current lack of transparency, the public and experts outside of the agency cannot trust that the processing of information, the risk of bias, and the concern for the general public health is being considered.

In the course of your November 2 statement, you acknowledged that there are available avenues to consider in the process of opioid approval that would give more consideration to the public health and that opioids pose unique risks. However, you failed to cite any evidence that the agency has taken into account these differences or any of the relevant National Academies recommendations in its decision-making for any specific drug, including Dsuvia.

You also referred to the need to eliminate “hurdles to product innovation.” Innovation must be focused not on more opioids, but on non-opioid analgesics. This could represent an entirely new class of analgesics bereft of addiction potential, respiratory depression, and other negative consequences.

Instead of explicitly encouraging opioid manufacturers to switch their research to the development of much less dangerous non-opioid alternatives for treating pain, the recent approval of Dsuvia does just the opposite: It holds out a financially rewarding approval carrot to companies for coming up with such allegedly “unique” but extremely dangerous new opioids.

This is a strategic error by the FDA with implications beyond considerations of individual drug formulations. Directing industry to introduce more opioids of any type, including new formulations such as Dsuvia, is inconsistent with the responsibility of the agency to protect public health and perpetuates the agency’s shirking of its duty to the public. This lack of thoughtful regulation represents an historic miscalculation, at best.

Over the last 25 years, the FDA has witnessed a loss of American lives of monumental proportions, directly attributable, in large part, to a single FDA-regulated drug class. It is the responsibility of the FDA to protect the American public from those opioids and any other drug class for which the harm, in many cases, is substantially greater than the benefit. Yet the agency continues to approve new potent opioids.

In a July 10, 2017, speech at the FDA’s Scientific Meeting on Opioids, you stated that “FDA has a clear legal and public health mandate to consider the safety of opioid drugs in terms of the risks and benefits of the labeled uses, as well as the risks associated with intentional or illicit misuse or abuse of the drugs.”⁹

⁹ Food and Drug Administration. Remarks by Scott Gottlieb delivered before the FDA’s Scientific Meeting on Opioids. July 10, 2017. <https://www.fda.gov/NewsEvents/Speeches/ucm566189.htm>. Accessed December 10, 2018.

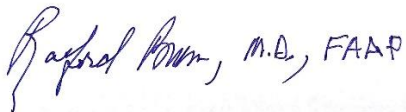
On November 2, when your agency approved Dsuvia, you stated that “*We won’t sidestep...* the question of whether or not America needs another powerful opioid while in the throes of a massive crisis of addiction.”

By citing non-existent unique Dsuvia benefits, but omitting mention of the risk of known diversion and life-threatening abuse of the previous intravenous version of sufentanil, you seem to have tried your best to justify its dangerous, unacceptable approval.

But by admitting that you had the “clear legal and public health mandate” to have rejected the drug but nevertheless approved it, you have clearly *sidestepped* “the question of whether or not America needs another powerful opioid while in the throes of a massive crisis of addiction” by answering “yes” instead of “no”.

Your July 10, 2017, comments and many others you have made concerning opioids demonstrate your awareness and ability to “talk the opioid talk.” But the reckless FDA decision to approve Dsuvia and the pitiful excuses you offered in your November 2 apologia exemplify that you have failed to provide FDA leadership to walk the necessary walk.

Sincerely,



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