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Citizen Petition

Requesting an Immediate Moratorium on the Approval of New Drug Applications for New Opioids or New Opioid Formulations

March 21, 2019

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide; Public Citizen's Health Research Group (HRG); HRG Founder and Senior Adviser, Sidney Wolfe, M.D.; and Raeford E. Brown, Jr, M.D., Professor of Anesthesiology and Pediatrics, University of Kentucky/Kentucky Children's Hospital and current Chair of the Food and Drug Administration's (FDA's) Anesthetic and Analgesic Drug Products Advisory Committee, the undersigned submit this petition under section 505 of the federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 355, and under FDA regulations at 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs immediately impose a moratorium on all future approvals of new drug applications (NDAs) for new opioids or new opioid formulations.

Petitioners seek this action because in the past two decades — most recently on November 2, 2018 — the FDA has approved new opioids or reformulations of existing opioids when previously known risks of the drugs exceeded their known benefits. These approvals violated the FDA's current drug approval requirements for ensuring safety and effectiveness and deviated from the principles articulated in the FDA's requested assessment of its opioid approval process by the National Academies of Sciences, Engineering, and Medicine (the National Academies), which concluded that the FDA had failed to adequately “incorporate public health considerations into opioid-related regulatory decisions.”¹

A. ACTIONS REQUESTED

Immediately impose a moratorium on approval of all NDAs for new opioids or new opioid formulations, not to be lifted until the FDA has implemented the elements recommended by the National Academies for inclusion in a currently non-existent opioid regulatory framework that is intended to prevent a continuation of dangerous past regulatory errors that clearly have contributed to the current deadly opioid crisis in the U.S.

¹ National Academies of Science, Engineering and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>.

B. STATEMENT OF GROUNDS

1. Background/overview

The stated purpose of the FDA is to be a science-based, regulatory agency with the core mission of protecting the public health.² To accomplish this, the agency is charged with, among other responsibilities, ensuring the safety and efficacy of prescription drugs.³ The process of new drug assessment and approval, established by the FDCA and FDA regulations, requires that the FDA review data and results of clinical trials, information about the drug's composition and manufacture, and other information.⁴ The FDCA directs that the FDA “refus[e] to approve” an application to market a new drug if the information is not sufficient to establish that the drug is safe and effective for use under the conditions suggested in the proposed labeling.⁵ The FDA's responsibility continues through the life cycle of the drug, as postmarket analysis of drug use behavior is also critical to protecting the public health after drug approval, and experience on the market may require withdrawal of the approval.⁶

In the period from 1997 through 2015, 263 opioid analgesic drug applications were approved by the FDA, including 41 NDAs and 222 abbreviated new drug applications.⁷ Of the 41 new opioid formulations approved by the FDA from 1997 through 2015, 27 — more than half (59 percent) — were approved during just the last seven years of this 19-year interval. Thus, the rate of FDA approvals of new opioid formulations actually accelerated while there was a rapid increase in the U.S. mortality rate due to the effects of opioids, both prescription and illicit.

The agency has never acknowledged the possible relationship between this increase and the approval of so many new opioid formulations in such a short period or publicly critiqued its role in approving any specific opioid drug that then contributed to this public health epidemic.

In March 2016, to better understand the opioid crisis and to determine if specific new actions by the agency were required to protect the public health, the FDA, headed by then-FDA Commissioner Robert Califf, asked the National Academies to convene an ad hoc committee of experts to, among other things, review the current status of FDA opioid regulation and to suggest improvements in it. Among the areas of focus in the FDA's charge to the committee, which was named the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, was input on “How to **formally** incorporate the broader public health impact of opioid abuse in future FDA approval decisions regarding opioids” [emphasis in original] and the

² Food and Drug Administration. What we do. <https://www.fda.gov/aboutfda/whatwedo/>. Accessed March 4, 2019; and Introduction: Women's health research roadmap. <https://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm478543.htm>. Accessed March 4, 2019.

³ 21 U.S.C. § 355(c)

⁴ 21 U.S.C. § 355(b).

⁵ 21 U.S.C. § 355(d).

⁶ 21 U.S.C. § 355(e).

⁷ Chai G, Xu J, Osterhout J et al. New opioid analgesic approvals and outpatient utilization of opioid analgesics in the United States, 1997 through 2015. *Anesthesiology*. 2018;128(5):953-966.

“public health consequences of any actions [the FDA] take(s) or could take with regard to opioid misuse, abuse, overdose, and death.”⁸

This need for the National Academies to help the FDA formulate a new opioid-specific regulatory framework also was discussed by the FDA’s senior leadership in an article in the *New England Journal of Medicine*: “We have asked the National Academy of Medicine...to help us develop a regulatory framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of abuse and misuse.”⁹

A comprehensive effort was undertaken by the National Academies, including engagement with many outside experts in the fields of public health, pharmacology, law, pharmacoepidemiology, and addiction medicine. This resulted in a report issued 19 months ago (July 2017) by the National Academies, with the major finding explicitly being that the FDA had failed to adequately “incorporate public health considerations into opioid-related regulatory decisions.” The National Academies therefore recommended many specific changes, compatible with the agency’s existing statutory authority, to be incorporated into a new FDA framework for opioid regulation that would address the agency’s long-standing deficiencies in this process.¹⁰

Now, almost three years after the FDA asked the National Academies for help to develop a new regulatory framework for opioid review, approval, and monitoring and more than 19 months after the National Academies’ conclusions and recommendations were published, the FDA, by its own admission, has failed to implement the National Academies’ recommendations for creating and implementing a new opioid regulatory framework.¹¹ Instead, the agency has added to the existing problem of too many opioids by continuing to approve new opioids without following its own legal mandates or addressing the National Academies’ concerns about the general public health.

In comments accompanying the agency’s approval of the latest opioid, Dsuvia (sufentanil sublingual tablet), on November 2, 2018, FDA Commissioner Gottlieb again described “a comprehensive process that the FDA has underway to develop a formal benefit and risk framework for how the agency evaluates the safety and efficacy of opioid medicines.”¹² Important elements of this much-needed process, using the agency’s existing statutory authority

⁸ Califf RM. FDA Charge to the committee: FDA opioid action plan and incorporating the broader public health impact into the formal risk-benefit assessment for opioids. Presentation to the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, National Academies of Sciences, Engineering, and Medicine. July 6, 2016. <http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/PublicHealth/PainResearch/FDA%20slides%207-6-2016.pdf>. Accessed March 4, 2019. Slide 21

⁹ Califf RM, Woodcock J, Ostroff S. A proactive response to prescription opioid abuse. *N Engl J Med*. 2016;374(15):1480-1485.

¹⁰ National Academies of Sciences, Engineering, and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>.

¹¹ Food and Drug Administration. Statment 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 March 4, 2019.

¹² *Ibid*.

to make the required changes, had been concisely laid out in the National Academies' report more than a year prior to the Commissioner's Dsuvia decision and comments.

The FDA's continued approval of new potent opioids, which are known to threaten the public health, without first significantly improving the review process by creating and finalizing an opioid regulatory framework recommended by the National Academies represents a clear and present continuing danger to the health and safety of people in this country. Until improvements are made, the FDA does not have a framework to effectively evaluate NDAs for new opioids and new opioid formulations to determine whether the legal standards for establishing safety and effectiveness are met. Thus, an immediate moratorium on opioid approvals is needed urgently. An opioid approval moratorium will allow the agency time and resources to use the information and recommendations from the National Academies' report to significantly tighten the regulatory process by creating an opioid regulatory framework that is based first and foremost on protection of the public health. During this moratorium, the pharmaceutical industry hopefully will increase its focus on developing potent non-opioid analgesic formulations that would dramatically reduce the risk of addiction and mortality while providing effective and safer analgesia.

We cite the approvals of Dsuvia and now-banned abuse-deterrent Opana ER as two representative examples of previous dangerous mistakes resulting from the FDA's deficient opioid regulatory process, which will inevitably be repeated without the proposed moratorium on opioid approvals lasting until a much-needed new opioid regulatory framework is created and implemented.

For each of these examples, we first cite the specific provisions of 21 U.S.C. § 355(d) (**Grounds for refusing application; approval of application; "substantial evidence" defined**) of the FDCA that, if used, should have caused the FDA to either reject these drugs or at least, in advance of approval, required better-designed studies to provide credible evidence to support effectiveness and safety, sufficient to evaluate the relative potential benefits and risks of harm of these opioids. We then cite specific recommendations and related commentary from the National Academies' opioid report and important elements for their suggested opioid regulatory framework that would have, using current FDCA statutory authority, required either the FDA to reject the drug based on existing evidence or the manufacturer to conduct more extensive and relevant studies prior to any possible approval.

We then review the FDA's actual regulatory approval process for each opioid, illustrating how current FDA laws, as well as the National Academies' recommendations — especially in the case of Dsuvia — were largely ignored to justify the approval of these unacceptably dangerous drugs, both of which lacked any unique benefit.

2. Example 1: The November 2, 2018, approval of Dsuvia, a sublingual, transmucosal formulation of sufentanil

a. Problems 1 and 2:

- **Inadequate inclusion of documented evidence of potential diversion and abuse**
- **Use of an opioid Risk Evaluation and Mitigation Strategy (REMS) to reduce off-label use and diversion/abuse that previously was shown to be ineffective with other highly potent opioids**

Relevant FDCA provisions at 21 U.S.C. § 355(d): “If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), *do not include adequate tests* by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof...*he shall issue an order refusing to approve the application.*” [emphasis added]

Relevant National Academies’ recommendation and related commentary:
“Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids. ... When...making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids... the FDA should explicitly consider...

- risks associated with existing and potential levels of diversion of all prescription opioids”¹³

“For drugs with the potential for misuse, for example, NDAs must include ‘studies or information related to abuse of the drug,’ which, of course, is not information about the use of the drug as directed in the proposed labeling. The FDA’s authority to consider the broad impact of its pre- and post-approval decisions on the health and well-being of American patients and consumers is an extension of the FDA’s primary role as a public health agency.”¹⁴

In the case of Dsuvia, the active ingredient sufentanil — which was approved by the FDA in 1984 as an intravenous formulation for general anesthesia — was first identified in 1990 as one of the leading opioid drugs of diversion and abuse by anesthesiologists.^{15,16,17} Case reports were published in 2004 involving three anesthesiologists who became addicted to sufentanil as a result of such diversion and abuse.¹⁸

Although this previously approved intravenous form of sufentanil has been available for use only under the tightest restrictions, it still has been shown to be a drug of diversion and abuse, leading to addiction and death, particularly among health care providers. Thus, assertions by AcetRx that

¹³ National Academies of Sciences, Engineering, and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>. p. 393.

¹⁴ *Ibid.* p. 381

¹⁵ Menk EJ, Baumgarten RK, Kingsley CP, et al. Success of reentry into anesthesiology training programs by residents with a history of substance abuse. *JAMA*. 1990;263(22):3060-3062.

¹⁶ 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.

¹⁷ Jungerman FS, Alves HN, Carmona MJ, et al. Anesthetic drug abuse by anesthesiologists. *Rev Bras Anesthesiol*. 2012;62(3):375-386.

¹⁸ Gold MS, Byars JA, Frost-Pineda K. Occupational exposure and addictions for physicians: case studies and theoretical implications.. *Psychiatr Clin N Am*. 2004; 27(4):745-753.

the careful risk-managed usage of Dsuvia in health care facilities would negate the risk of diversion and death are unfounded.

The analysis of the safety of Dsuvia, as presented by the FDA and AcclRx at the October 12, 2018, meeting of the Anesthetic and Analgesic Drug Products Advisory Committee did not include any information about these previously identified and published risks of intravenous sufentanil diversion and abuse by health care professionals despite it being, as recommended by the National Academies' report, within the FDA's public health authority to require such information. Therefore, the analysis of the safety of the sublingual formulation of sufentanil is dangerously incomplete.

A further problem with the dangerous opioid Dsuvia is that its approval was predicated on the existence of a successful opioid REMS proposed by the sponsor and the FDA. Such previous opioid REMS have been shown to be unsuccessful in preventing off-label use.¹⁹

During an August 3, 2018, joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee — two months before the latter committee voted in favor of approving Dsuvia — data presented by the FDA revealed the failure of the transmucosal immediate-release fentanyl (TIRF) REMS, the most rigorous such opioid REMS safety program created to date. The TIRF REMS was created to provide safe use of TIRF products by limiting prescribing of them to breakthrough pain in cancer patients, and to ensure that, because of the inherent risks of these potent drugs, only opioid-tolerant patients would be prescribed these products. Subsequent FDA analysis demonstrated that this REMS risk mitigation had been ineffective.

The FDA had stated that these drugs are only approved “for the management of breakthrough pain in adults with cancer who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain”²⁰ [emphasis added]. The limitation to breakthrough cancer pain is based on the serious risks of these transmucosal fentanyl products, which greatly outweigh the benefits for noncancer patients. The additional limitation to patients who are opioid-tolerant is meant to avoid the much greater, life-threatening risks of severe respiratory depression or death in opioid-naïve patients who are much more likely to experience such serious harms because of their inability to tolerate the doses of high-potency opioids found in TIRF products.

According to the FDA, nearly 60 percent of prescriptions for TIRFs were for patients without cancer, where having cancer was defined very broadly as having received a cancer diagnosis within five years of the prescription claim.²¹ Equally unsatisfactory and dangerous, the FDA

¹⁹ A REMS is a safety strategy used by the FDA “to manage a known or potentially serious risk associated with a medicine to enable patients to have continued access to such medicines by managing their safe use.” See Food and Drug Administration. Risk evaluation and mitigation strategies (REMS). February 2, 2018. <https://www.fda.gov/Drugs/DrugSafety/REMS/default.htm>. Accessed March 4, 2019.

²⁰ Food and Drug Administration. FDA 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 March 4, 2019. PDF p. 5.

²¹ Food and Drug Administration. Transcript of the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee. August 3, 2018.

presented evidence that 42 percent of patients who start a TIRF medicine are opioid nontolerant, as determined by claims-based algorithm.²²

The view for many of the assembled members of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee at that earlier, August 3, 2018 meeting was that the TIRF opioid REMS was a failed process. This was summarized in the minutes of the meeting: “The committees agreed that based on the data available, TIRF medications are being prescribed to patients who are non-cancer patients and who are not opioid tolerant.”²³

b. Problem 3: Inadequate evidence to justify Dsuvia’s major FDA-approved indication: “indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the *management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate*”²⁴ [emphasis added]

Relevant FDCA provisions at 21 U.S.C. § 355(d): “If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that... (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, *there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.....he shall issue an order refusing to approve the application*”[emphasis added].

Relevant National Academies recommendation and related commentary:
Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations. To utilize a systems approach that adequately assesses the public health benefits and risks described in Recommendation 6-1, the [FDA] should continue to require safety and efficacy evidence from well-designed clinical trials...²⁵

“The investigational drug evaluation process also has important limitations, particularly with respect to the approval of opioids.

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM623142.pdf>. Accessed March 4, 2019. PDF p. 229

²² Food and Drug Administration. FDA 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 March 4, 2019. PDF p. 100.

²³ Food and Drug Administration. Summary minutes of the joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee. August 3, 2018. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM620615.pdf>. PDF p. 6.

²⁴ AcelRx Pharmaceuticals. Label: sufentanil (DSUVIA). November 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209128s000lbl.pdf. Accessed March 4, 2019.

²⁵ National Academies of Sciences, Engineering, and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>. p. 397.

“For example, showing that a drug has substantial evidence of efficacy does not necessarily mean that the drug is more effective than currently available therapies, or that the efficacy demonstrated is clinically meaningful...

“In addition, clinical trials sufficient to meet the FDA’s efficacy standard can be conducted in a brief, highly protocolized setting and often exclude many patients who would be expected to get the drug following its approval.”²⁶

As stated in the FDA-approved label, Dsuvia is indicated for the “management of acute pain severe enough to require an opioid and for which alternative treatments are inadequate.”

The major controlled study that the FDA relied on for approval involved patients who had just undergone abdominal surgery. In the Dsuvia-treated subjects, the median time before they reported clinically meaningful pain relief was 54 minutes.²⁷ Because no active comparator drug was used in the study, 54 minutes was somewhat, but not statistically significantly, sooner than the median time to onset of clinically meaningful pain relief in subjects given a placebo, clearly falling short of adequate management of severe pain. Multiple alternative opioid treatments would not have required patients to wait almost an hour for meaningful relief of acute postoperative pain. All of the controlled studies upon which the FDA’s approval of Dsuvia was based were placebo-controlled; none used a comparator opioid or non-opioid analgesic that could establish whether Dsuvia was even as good as alternative treatments.

Thus, under the FDA’s existing legal authority and consistent with the National Academies’ recommendations and conclusions, the inadequate effectiveness data from the premarket studies discussed above provided sufficient grounds for the FDA to reject Dsuvia. Furthermore, in addition to failing to establish the effectiveness for the approved indication, the public health risks presented by the drug significantly outweigh its established benefits.

c. Problem 4: Failure to require drug efficacy or safety testing for a major proposed use – injured soldiers in the battlefield

Relevant FDCA provisions at 21 U.S.C. § 355(d): “If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that... (2) the results of such tests show that such drug is unsafe for use under such conditions *or do not show that such drug is safe for use under such conditions*;... (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, *he has insufficient information to determine whether such drug is safe for use under such conditions*; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, *there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed,*

²⁶ *Ibid.* P. 364.

²⁷ AcclRx Pharmaceuticals. Label: sufentanil (DSUVIA). November 2018.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209128s0001b1.pdf. Accessed March 4, 2019.

recommended, or suggested in the proposed labeling thereof *he shall issue an order refusing to approve the application*”[emphasis added].

Relevant National Academies Recommendation: **Recommendation 6-2 (see above).**

The FDA’s regulatory authority cited above and the National Academies’ recommendation for a thorough public health-oriented analysis of benefits and risks were certainly not used by the agency in considering the approval of Dsuvia. Not only did the premarket studies fail to demonstrate a prompt, meaningful benefit in relieving acute postoperative pain, as discussed above, but the proposal of battleground use in injured soldiers raises further safety concerns about possible diversion and abuse.

The development of this sublingual formulation of sufentanil was supported, in part, by the Department of Defense (DOD) through a contract with AcelRx Pharmaceuticals as an alternative to intravenous formulations of opioid analgesics for soldiers injured on the battlefield.²⁸ Even though the FDA-approved label for Dsuvia does not contain any statement that it is indicated for battlefield use,²⁹ on November 2, 2018, the day the drug was approved, FDA Commissioner Gottlieb nevertheless stated that a unique use for Dsuvia “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.”³⁰

In contrast, at the October 12, 2018, meeting of the FDA’s Anesthetic and Analgesic Drug Products Advisory Committee regarding Dsuvia, Dr. Pamela Palmer, Cofounder and Chief Medical Officer of AcelRx Pharmaceuticals, acknowledged the following: “So as far as where we’re distributing, [Dsuvia] would be going to a military hospital, and that would qualify under the REMS. And we have been notified by the Department of Defense that they will be following our REMS.”³¹ However, in response to a question during the advisory committee meeting about whether the DOD accepted Dsuvia as a good product for the battlefield, Dr. Palmer stated that the DOD officials are “excited, from our communications with them, to have this product.”³² When pressed further about whether DOD officials “accept DSUVIA as you’ve developed [it],” Dr. Palmer responded “Yes.”³³

²⁸ 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 March 4, 2019.

²⁹ AcelRx Pharmaceuticals. Label: sufentanil (DSUVIA). November 2018.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209128s000lbl.pdf. Accessed March 4, 2019.

³⁰ 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 March 4, 2019.

³¹ Food and Drug Administration. Transcript of the meeting of the Anesthetic and Analgesic Drug Products Advisory Committee. October 12, 2018.

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM629601.pdf>. Accessed March 5, 2019. PDF p. 90.

³² *Ibid.* PDF pp. 184-186.

³³ *Ibid.* PDF p. 186.

However, the company's NDA for Dsuvia was not supported by any controlled clinical trials involving major trauma patients whose injuries would mimic battlefield injuries.³⁴ As mentioned above, even in a study of postoperative patients who had abdominal surgery, the median onset of meaningful pain relief with Dsuvia was 54 minutes, inconsistent with the requirement of analgesia for either major battlefield trauma or, as mentioned above, for postoperative pain relief. This lack of a meaningfully timely clinical effect is inconsistent with the needs for medics treating soldiers with major trauma on the battlefield or of physicians caring for nonbattlefield patients with major trauma.

Thus, there would be no basis for the DOD to be excited about Dsuvia for use on the battlefield, as suggested by Dr. Palmer, because it has not been shown to be safe and effective in the setting of battlefield injuries; in fact, the evidence suggests otherwise. Furthermore, it's unclear whether DOD officials appreciated the problems with the drug.

Dr. Palmer's comment that the product was to be distributed to military hospitals subject to REMS also fails to address the risks of diversion of the opioid in the battlefield. The FDA-approved product label states that Dsuvia is for "use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments" because in those settings tight controls theoretically could be in place to reduce the chance of diversion and abuse. The idea that a battlefield setting could have such tight controls is absurd.

3. Example 2: The 2011 approval of reformulated Opana ER, followed by years of inaction

a. Problems:

- **Failure of the FDA to appropriately consider documented evidence of high potential for diversion and intravenous abuse, available when the agency approved reformulated Opana ER**
- **Failure of the FDA to promptly act to remove Opana ER from the market once it was presented with evidence of a public health emergency due to diversion and intravenous abuse of the drug**

Relevant FDCA provisions at 21 U.S.C. § 355(d): "If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), *do not include adequate tests* by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof...*he shall issue an order refusing to approve the application*" [emphasis added].

Relevant National Academies recommendation and related commentary:
Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a

³⁴ Food and Drug Administration. Clinical review(s) for application number: 209128Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/209128Orig1s000MedR.pdf. Accessed March 5, 2019. PDF pp. 49-50. No controlled clinical trials involving major trauma patients were described in the clinical review(s) included in the approval package.

comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids. The agency should use this approach, in conjunction with advisory committee input, to evaluate every aspect of its oversight of prescription opioid products in order to ensure that opioids are safely prescribed to patients with legitimate pain needs and that, as actually used, the drugs provide benefits that clearly outweigh their harms. When... making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids; and monitoring opioids on the U.S. market, the FDA should explicitly consider...

- risks associated with existing and potential levels of diversion of all prescription opioids;
- risks associated with the transition to illicit opioids (e.g., heroin), including unsafe routes of administration, injection-related harms (e.g., HIV and hepatitis C virus), and OUD [opioid use disorder].³⁵

“For drugs with the potential for misuse, for example, NDAs must include ‘studies or information related to abuse of the drug,’ which, of course, is not information about the use of the drug as directed in the proposed labeling. The FDA’s authority to consider the broad impact of its pre- and post-approval decisions on the health and well-being of American patients and consumers is an extension of the FDA’s primary role as a public health agency.”³⁶

In 2006, the FDA approved Endo Pharmaceuticals’ Opana ER, an extended-release version of oxymorphone. According to the FDA, this new opioid formulation was “Not intended to be abuse deterrent”³⁷ [emphasis in original]. The drug was to be swallowed whole, and “[c]rushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose significant risk that could result in overdose and death.”³⁸

Then, in 2010, Endo Pharmaceuticals submitted to the FDA an NDA for a reformulated version of Opana ER that was purported to have physicochemical properties expected to deter abuse by the intranasal and intravenous route.³⁹

When the FDA wrongly approved the reformulated version of Opana ER on December 9, 2011, and allowed it to remain on the market until 2017, it failed to take into account available studies and information related to the potential abuse of the drug and the broad impact of its preapproval and postapproval decisions regarding the drug on the health and well-being of American patients, as the National Academies would subsequently recommend in 2017. The obvious lessons that

³⁵ National Academies of Sciences, Engineering, and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>. p. 393.

³⁶ *Ibid.* p. 381

³⁷ Food and Drug Administration. FDA slides for the March 13-14, 2017, 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/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf>. Accessed March 5, 2019. PDF p.8.

³⁸ *Ibid.* PDF p.8.

³⁹ *Ibid.* PDF p.9.

should have prompted Dsuvia's rejection by the FDA clearly were not learned from the disastrous and unacceptable approval of reformulated Opana ER, a reformulation that actually increased intravenous abuse, later necessitating market withdrawal of the drug, as reviewed in detail below.

b. Review of the FDA's preapproval awareness of evidence of potential intravenous Opana ER abuse that should have led to rejection of the drug, followed by 6½ years of inaction thereafter

i. December 22, 2010: FDA biopharmaceutics review portion of the FDA's Cross-Discipline Team Leader Review

Dr. Sandra Sharp [FDA biopharmaceutics reviewer] notes in her review of the reformulated Opana ER's tamper-resistant characteristics "that [Opana ER] does not show good resistance to tampering employed by recreational or experienced abusers, as evidenced by a 60% increase in the dissolution in one hour for tablets [redacted] compared to intact tablets."⁴⁰

ii. December 9, 2011: FDA final approval package for reformulated Opana ER

Based on preapproval laboratory studies to determine whether reformulated Opana ER could be tampered with and thereby abused, the FDA concluded that "[w]hile the new formulation has demonstrated a minimal improvement in resistance to tampering by crushing, thereby limiting the likelihood of abuse by crushing followed by ingestion and [intranasal] insufflation (snorting) to some degree, it can still be [redacted], cut [redacted] rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation."⁴¹

In an in vitro manipulability experiment conducted before approval, the greatly increased ability to extract soluble oxymorphone that could be abused by the injection route from the reformulated Opana ER in comparison with the initial 2006 formulation of Opana ER was documented.⁴²

⁴⁰ Food and Drug Administration. Cross-Discipline Team Leader review for NDA 201655, Oxymorphone HCL extended-release tablets. December 22, 2010. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000MedR.pdf. Accessed March 5, 2019. PDF p. 23.

⁴¹ Food and Drug Administration. Summary review for for NDA 201655, Oxymorphone HCL extended-release tablets. December 9, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000SumR.pdf. Accessed March 5, 2019. PDF pp. 4-5.

⁴² Food and Drug Administration. FDA slides for the March 13-14, 2017, 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/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf>. Accessed March 5, 2019. PDF p. 24.

Entry	Product	Manipulation	Withdrawn	% API
1	Original Opana ER	crushed	0.3 g	0.4%
2	Reformulated Opana ER	flattened	4.23 g	26%

www.fda.gov

NDA 201-655 07/07/2010

API = Active Pharmaceutical Ingredient--Oxymorphone HCl for Opana.

This preapproval manipulability experiment involved physical manipulation of the tablets and dissolution for subsequent syringe withdrawal of the active ingredient from the reformulated Opana ER compared with the original Opana ER. The results were that extraction yielded 65 times more active soluble ingredient from reformulated Opana ER than from the original formulation (26 percent versus 0.4 percent).

iii. FDA failure to have a preapproval advisory committee meeting because there were “no unusual concerns regarding the efficacy or safety of this reformulated opioid.”

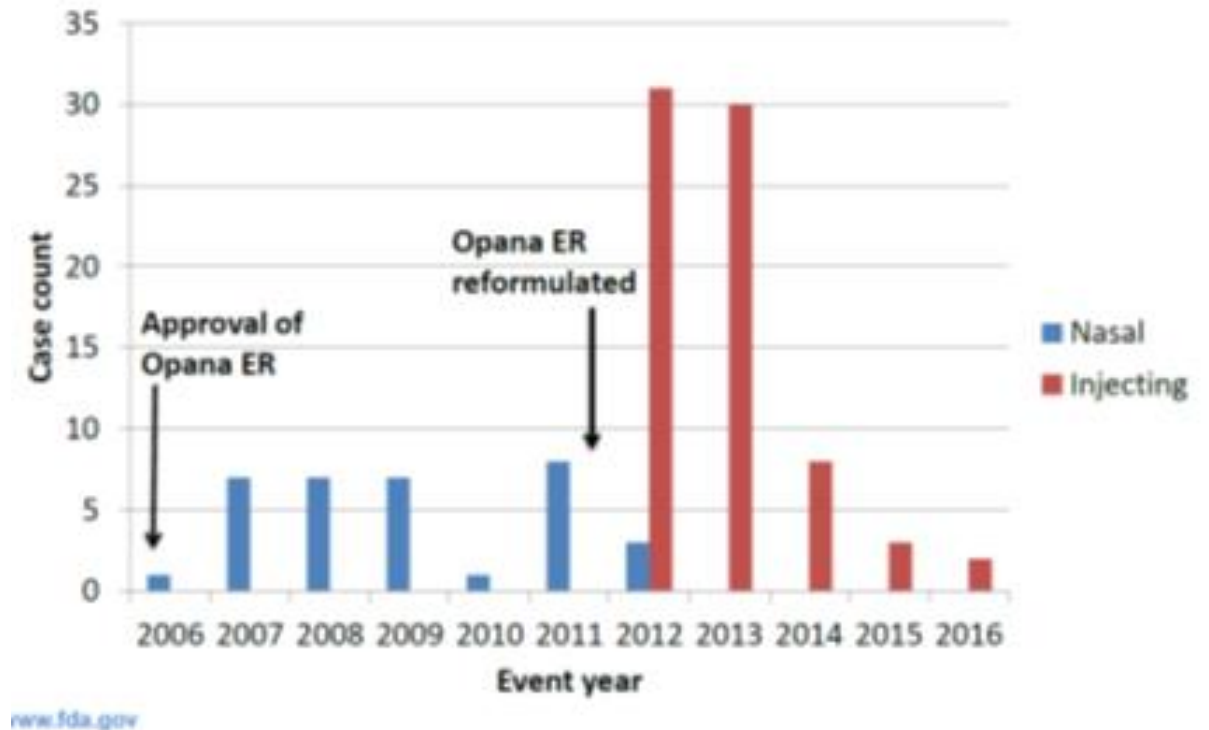
Despite these serious preapproval safety findings, the FDA’s summary review in the approval package explains that no advisory committee was convened before the approval because “there were no unusual concerns regarding the efficacy or safety of this reformulated opioid.”⁴³ This inexcusable and demonstrably false statement is contradicted by the data showing the increased extractability of active oxymorphone from the reformulated Opana ER that made the drug more susceptible to intravenous abuse, facts that were well-known to the FDA before approval. (The FDA’s decision not convene an advisory committee to consider the NDA for the reformulated Opana ER presages the agency’s decision to disinvite most members of its Drug Safety and Risk Management Advisory Committee to the October 12, 2018, advisory committee meeting concerning Dsuvia.)

Had the aforementioned preapproval FDA assessments, concluding that reformulated Opana ER could be rendered “readily abusable” by intravenous injection despite its concomitantly slightly limited potential for nasal abuse, been taken seriously (which would have been more likely if there had been an advisory committee meeting focusing on the increased risk of serious intravenous abusability), the drug likely would not have been approved. The preapproval preponderance of nasal abuse of nonreformulated Opana ER would not then have transformed into the postapproval documented epidemic of injection abuse with reformulated Opana ER.

The following data, relevant to this preventable outcome, were presented at the March 13, 2017, FDA advisory committee meeting concerning reformulated Opana ER:

⁴³ Food and Drug Administration. Summary review for for NDA 201655, Oxymorphone HCL extended-release tablets. December 9, 2011. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201655Orig1s000SumR.pdf. Accessed March 5, 2019. PDF p. 7.

FAERS Cases of Non-Oral Abuse of Opana ER Reporting Event Dates



The above figure shows that all of the 31 non-oral Opana ER abuse cases reported to the FDA before Opana ER reformulation involved nasal abuse.⁴⁴ After reformulation, 74 of the 77 subsequently reported cases involved injection abuse; the three nasal cases were reported in the first year of transition from the original to the reformulated version. By the end of 2012 — the first year after approval of the reformulated Opana ER — 31 cases of injection abuse of the drug had already been reported to the FDA.

iv. May 10, 2013, FDA letter to Endo Pharmaceuticals (17 months after approval of reformulated Opana ER and more than four years before the FDA’s delayed market removal)

In a May 10, 2013, letter to Endo Pharmaceuticals, the FDA stated that postmarketing data from Opana ER investigations “appear to suggest that a greater (and rising) percentage of Opana ER abusers are abusing Opana ER via injection since the replacement of OP [the original formulation of the drug approved in 2006] with OPR [the reformulated Opana ER approved in 2011] in the market. This suggestion would be consistent with [the premarket] in vitro data

⁴⁴ Food and Drug Administration. FDA slides for the March 13-14, 2017, 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/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf>. Accessed March 5, 2019. PDF p. 64.

showing that while it may be more challenging to prepare OPR for insufflation [intranasal abuse] using certain tools (although it is possible to do so using other tools), it may be *easier* [emphasis added] to prepare OPR for injection. Taken together, these data suggest the troubling possibility that the reformulation may be shifting a non-trivial amount of Opana ER abuse from snorting to even more dangerous abuse by intravenous or subcutaneous injection.”⁴⁵

The FDA’s letter also stated, “Abuse via injection is highly dangerous, and injection of OPR in particular has been associated with a serious thrombotic thrombocytopenic purpura (TTP)-like illness... TTP is a serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia. FDA's review has not revealed this association with any other opioid analgesic.”⁴⁶

As reported by the FDA, the occurrence of a thrombotic microangiopathy (TMA), a broader category of hematologic disease which includes TTP, appears to be most commonly linked to patients who used reformulated Opana ER. As shown below, the FDA identified 59 cases of TMA in the FDA Adverse Event Reporting System (FAERS) database from December 2011 (when reformulated Opana ER was approved through June 2016).⁴⁷

Thrombotic Microangiopathy

- FAERS search
 - Opana ER
 - Reports initially received: approval* – June 1, 2016
 - MedDRA (version 19.0) high level group terms:
 - Coagulopathies and bleeding diatheses, Haemolyses and related conditions, Haematological disorders, and Platelet disorders

TMA: FAERS Case Series	
Review Period	FAERS Cases
Dec 2011* – Mar 2013	29
Mar 2013 – Jun 2016	30

www.fda.gov

* Reformulated Opana ER was approved December 9, 2011

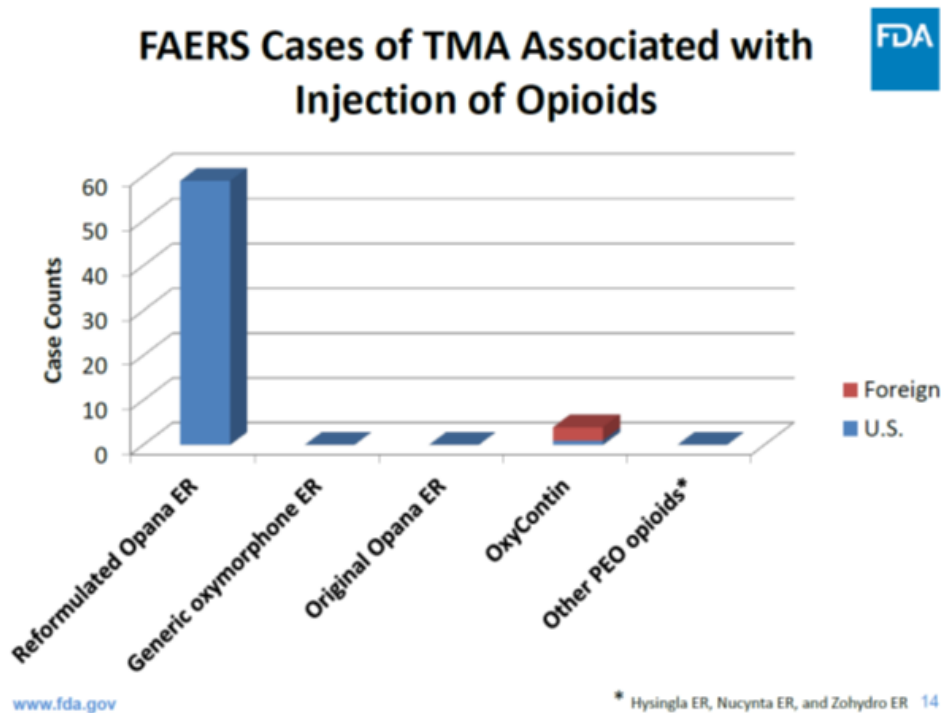
11

⁴⁵ Food and Drug Administration. Letter to Endo Pharmaceuticals. May 10, 2013. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM545760.pdf>. Accessed March 5, 2019. PDF p. 76, footnote 25.

⁴⁶ *Ibid.* PDF pp. 74-75, footnote 21.

⁴⁷ Food and Drug Administration. FDA slides for the March 13-14, 2017, 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/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf>. Accessed March 5, 2019. PDF p. 68.

The FDA further reported that these TMA cases were rarely associated with any opioids other than reformulated Opana ER, as shown in the figure below:⁴⁸



v. 2014-2015: HIV and hepatitis C outbreak caused by reformulated Opana ER

At the March 13-14, 2017, joint meeting of the FDA’s Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee, further data highlighting the harms that resulted from the reckless FDA approval of the reformulated Opana ER were reviewed, and the advisory committees eventually voted 18 to 8 (with one abstention) that the risks of the drug outweighed its benefits.⁴⁹

Most notably, a large HIV infection outbreak had occurred in 2014-2015 in a non-urban region of southeastern Indiana that was closely linked with the injection of oxymorphone extracted from reformulated Opana ER, as documented in the figure below.⁵⁰

⁴⁸ *Ibid.* PDF p. 71.

⁴⁹ Food and Drug Administration. Summary minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee joint meeting. March 13-14, 2017. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf>. Accessed March 5, 2019. PDF p. 8.

⁵⁰ Peters PJ, Pontones P, Hoover KW, et al. HIV infection linked to injection use of oxymorphone in Indiana, 2014–2015. *N Engl J Med.* 2016;375(3):229-239.

B HIV Diagnoses According to Week of Testing

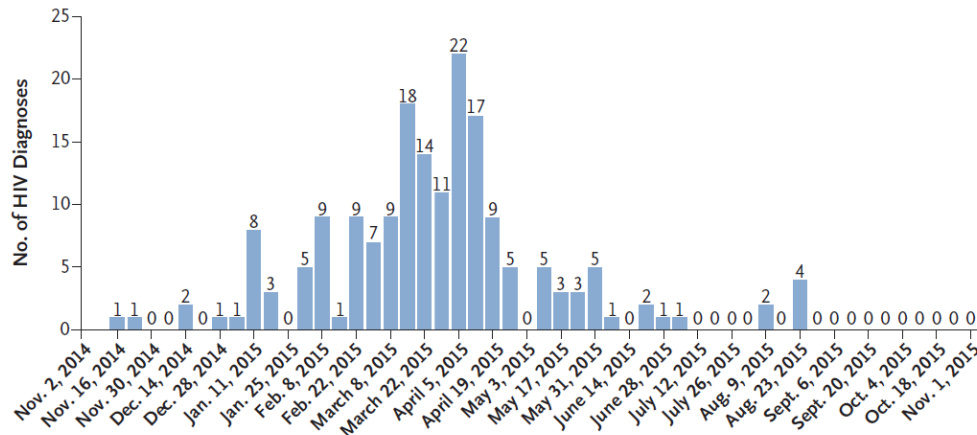


Figure 1. Outbreak of HIV Infection in Southeastern Indiana.

A team of investigators led by the Indiana State Department of Health and the Centers for Disease Control and Prevention (CDC) documented the outbreak of HIV infections among residents of the small rural community of Scott County in Indiana. From November 18, 2014, to November 1, 2015, HIV infection was diagnosed in 181 case patients. Most of these patients (87.8%) reported having injected the extended-release formulation of Opana ER and 92.3% were coinfecting with hepatitis C virus.⁵¹

During the March 13-14, 2017, joint FDA advisory committee meeting regarding Opana ER, CDC physician Dr. John Brooks attested to the fact that the affected patients were accurately identifying reformulated Opana ER as the more abusable form of oxymorphone rather than generic versions of nonreformulated oxymorphone. Dr. Brooks reported that interviews with a representative sample of the HIV-infected patients from the Indiana outbreak revealed that “this community was very, very knowledgeable about the drug of choice that they were using, [reformulated] Opana ER. And almost every person we interviewed could accurately describe the tablet. It was a biconvex yellow tablet with the number 40 imprinted on it.”⁵²

Additional data from the National Survey on Drug Use and Health (NSDUH) that was presented by the FDA at the March 13-14, 2017, joint advisory committee meeting regarding Opana ER showed that in 2015, oxymorphone was misused by 28.9% of users during the preceding year, a proportion that was almost twice that for users of either fentanyl or oxycodone and almost three times greater than that for users of morphine (see table below).⁵³ Of note, for the 2015 NSDUH,

⁵¹ *Ibid.*

⁵² Food and Drug Administration. Transcript of the March 13, 2017, open session of the joint meeting of Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee.

<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM553190.pdf>. Accessed March 5, 2019. PDF p. 226.

⁵³ Food and Drug Administration. FDA slides for the March 13-14, 2017, 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/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf>. Accessed March 5, 2019. PDF pp. 151-152. The FDA described the NSDUH as follows: a nationally representative household survey that provides estimates on the use and misuse of various types of drugs in the United States, including prescription pain relievers. The survey uses pill

the definition of misuse included important components of abuse as well: “use in any way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.”⁵⁴

NSDUH

Estimated Use and Misuse of Prescription Pain Relievers* among Persons Age 12 Years or older, 2015



	Any Use in Past year: N, in thousands (S.E. **)	Misuse in Past Year: N, in thousands (S.E.)	Misuse among Past Year Any Users: % (S.E.)
Hydrocodone	58,261 (688)	7,193 (229)	12.3 (0.38)
Oxycodone	27,873 (503)	4,258 (169)	15.2 (0.57)
Tramadol	18,573 (440)	1,794 (124)	9.7 (0.63)
Morphine	7,205 (257)	697 (64)	9.7 (0.87)
Fentanyl	1,997 (138)	299 (42)	15.0 (2.05)
Demerol®	1,434 (125)	106 (23)	7.4 (1.59)
Oxymorphone	1,329 (114)	384 (49)	28.9 (3.44)
Hydromorphone	2,484 (161)	261 (39)	10.5 (1.55)

*Methadone and buprenorphine are not included, as these categories include products used to treat opioid use disorders

**S.E. = Standard Error

Source: Table generated by reviewer using data from “Results from the 2015 NSDUH: Detailed Tables,” Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, September 8, 2016

The gist of the FDA’s belated concerns about the reformulated Opana ER-caused public health disaster were summed up in the following FDA slide:⁵⁵

photo cards to assist in the identification of the drugs, and the results from the redesigned 2015 survey now allow comparisons with past year use and misuse across opioid subgroups.

⁵⁴ Hughes A, Williams MR, Lipari RN, et al. Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Agency. NSDUH Data Review. September 2016. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.pdf>. Accessed March 6, 2019. PDF p. 1.

⁵⁵ Food and Drug Administration. FDA slides for the March 13-14, 2017, 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/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547235.pdf>. Accessed March 5, 2019. PDF p. 73.

Summary

Non-oral abuse of Opana ER before and after reformulation

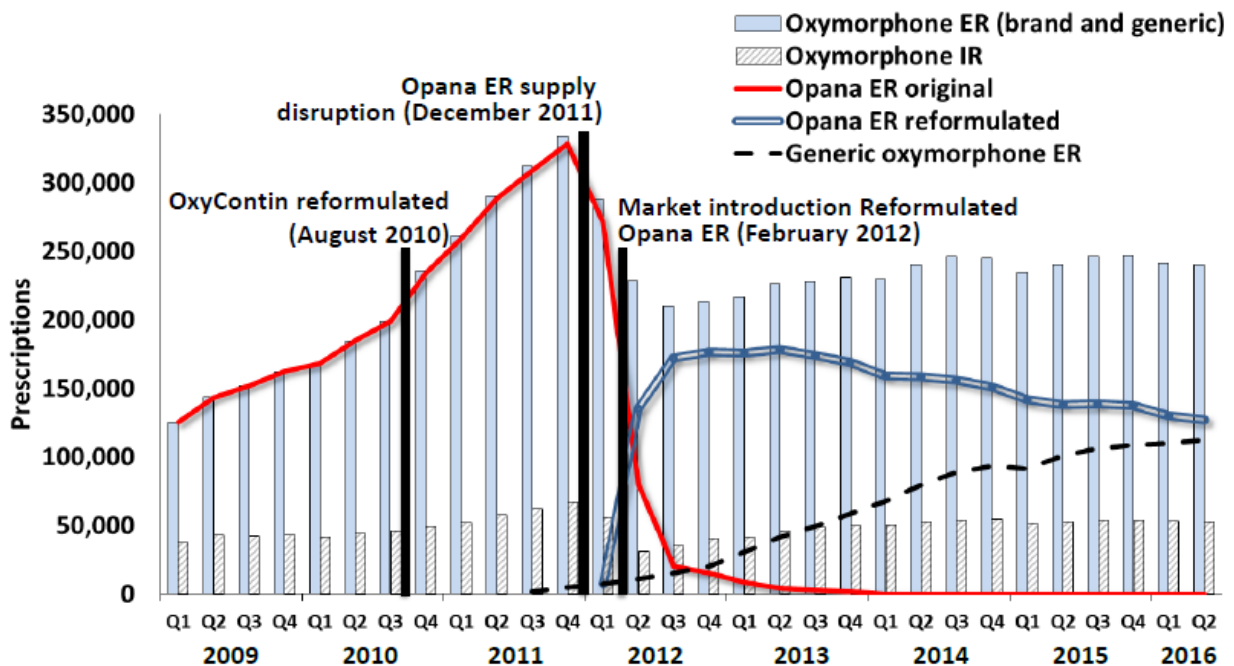
- Shift in route of abuse from nasal to injection following reformulation

As estimated from the figure below, from the time when the reformulated Opana ER was approved by the FDA in December 2011 through the second quarter of 2016 — one year before the agency’s inexcusably delayed request to Endo Pharmaceuticals to withdraw the drug from the market — well over 2.4 million prescriptions for reformulated Opana ER were filled in the U.S.⁵⁶

Oxymorphone Prescriptions



Nationally Estimated Number of Dispensed Prescriptions for Oxymorphone ER and Oxymorphone IR products from U.S. Outpatient Retail Pharmacies



www.fda.gov

Source: IMS Health, National Prescription Audit™. Data Extracted September 2016.

7

c. Critique of the FDA’s June 8, 2017, press release announcing the agency’s request that the reformulated Opana ER be removed from the market because of risks related to abuse

In a June 8, 2017, press release announcing the FDA’s request that Endo Pharmaceuticals withdraw reformulated Opana ER, the agency was unwilling to accept any responsibility for its reckless December 2011 approval of the drug, despite previous FDA-acknowledged evidence

⁵⁶ *Ibid.* PDF p. 50.

about its potential for injection abuse, or its more than six-year delay after approval in removing it from the market.

The following excerpts from the FDA's June 8, 2017, press release announcing that the agency had requested removal of reformulated Opana ER from the market for risks related to abuse⁵⁷ are striking in their repeated claims of FDA blamelessness. Each is followed by our brief comments.

FDA statement: "After careful consideration, the agency is seeking removal based on its concern that the benefits of the drug may no longer outweigh its risks."

Our response: In the chronology above, "careful consideration" of known facts should have prevented approval of the drug or prompted the agency's call for withdrawal at least four years before it occurred.

FDA statement: "We are facing an opioid epidemic – a public health crisis, and we must take all necessary steps to reduce the scope of opioid misuse and abuse," said FDA Commissioner Scott Gottlieb, M.D. "We will continue to take regulatory steps when we see situations where an opioid product's risks outweigh its benefits, not only for its intended patient population but also in regard to its potential for misuse and abuse."

Our response: The empty rhetoric of this statement begins with the dangerously belated steps actually taken by the FDA concerning misuse and abuse of reformulated Opana ER and ends 17 months later with a repeat in the form of the November 2018 approval of Dsuvia. Although Drs. Gottlieb and Janet Woodcock talk of "continu[ing] to take regulatory steps," they are actually continuing not to take necessary regulatory steps.

FDA statement: "The FDA's decision is based on a review of all available postmarketing data, which demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following the product's reformulation."

The FDA conveniently avoids any mention of the alarming premarket studies that showed the increased extractability of active oxymorphone from the reformulated Opana ER that made the drug more susceptible to intravenous abuse than the original formulation. These findings provide more than sufficient basis for non-approval of the drug, had the agency followed the precautionary principle of public health.

FDA statement: "While the product met the regulatory standards for approval, the FDA determined that the data did not show that the reformulation could be expected to

⁵⁷ Food and Drug Administration. FDA news release: FDA requests removal of Opana ER for risks related to abuse. June 8, 2017. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm>. Accessed March 6, 2019.

meaningfully reduce abuse and declined the company's request to include labeling describing potentially abuse-deterrent properties for Opana ER.”

Our response: Although correct in refusing to allow Endo Pharmaceuticals to make abuse-deterrent claims for the reformulated Opana ER in 2017, FDA rejection of the NDA for the drug in 2011 because of the clear premarket evidence of its *abuse-enhancing* properties would have constituted a public health-oriented decision, rather than an Endo Pharmaceuticals-oriented decision.

FDA statement: ““When we determined that the product had dangerous unintended consequences, we made a decision to request its withdrawal from the market,”” said Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research. ‘This action will protect the public from further potential for misuse and abuse of this product.’”

Our response: There is unequivocal evidence that Dr. Woodcock’s perception of what constituted timely regulatory action in the case of the reformulated Opana ER is dangerously off-target and irresponsible. The FDA had data prior to approval indicating that the drug would be more susceptible to intravenous abuse and documented evidence of the subsequent, predictable harm actually caused by reformulated Opana ER for more than four years prior to considering withdrawal of the drug from the market.

In summary, as is the case with Dsuvia, there was never sufficient evidence to justify the approval of reformulated Opana ER. There was preapproval evidence that the drug was unsafe. An opioid regulatory framework that incorporates public health considerations, such as that proposed by the National Academies, would have precluded approval of the drug in the first place and would have prompted a much faster withdrawal once it was on the market.

4. The National Academies recommendation 6-6 warrants a moratorium before continuing to approve more dangerous opioids

In addition to the National Academies recommendations previously discussed in the context of the FDA’s regulatory decisions for Dsuvia and reformulated Opana ER, another key recommendation in the National Academies’ opioid report was the following:

Recommendation 6-6, Conduct a full review of currently marketed/approved opioids. To consistently carry out its public health mission with respect to opioid approval and monitoring, the U.S. Food and Drug Administration should develop a process for reviewing, and complete a review of, the safety and effectiveness of all approved opioids, utilizing the systems approach described in Recommendation 6-1.⁵⁸

⁵⁸ National Academies of Sciences, Engineering, and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>. p. 409.

The report proposed that the review contemplated in the above recommendation would be accomplished by “an expert [independent] panel that would systematically examine the current range of approved brand-name and generic opioids to determine which of these drugs remained effective and safe.” The report concluded that this “process might lead to the removal of some of the opioid formulations or doses currently on the market because it is highly unlikely that all of these products would be judged safe and effective under the new drug approval framework proposed in this chapter should they just now be entering the market.”⁵⁹

There is already substantial outside agreement about the public health risks incurred from the approval process that led to the marketing of Oxcontin, including outside agreement that the agency has not taken responsibility for the harms that occurred. Unfortunately, the lax method of FDA approval, the lack of transparency, and the failure to value the public health over the fiscal health of the pharmaceutical industry has not changed.

The National Academies-recommended review of all currently approved opioids further justifies the urgent need for a moratorium on approving any new opioids. The framework proposed in the National Academies’ report for better, safer regulation of opioids cannot be completed without first documenting the detailed history of the FDA’s other past mistakes. Development of the details of the framework must be informed by these past mistakes, none of which the FDA has ever publicly acknowledged. Only in this manner will the new framework be constructed in such a way that will prevent a repeat of these mistakes. The National Academies-suggested removal of those opioids that would no longer be considered safe and effective under the more public health-oriented framework would be another benefit of the requested moratorium.

This review of prior opioid approvals is critical to remove the specter of past regulatory failures and to gain the confidence of the American public. Obviously, an internal FDA review using the current regulatory process or one carried out by the pharmaceutical industry itself would be biased. Therefore, an independent entity would be required to ensure complete transparency. Fifty years ago this was accomplished through the work of the National Academy of Sciences and the National Research Council’s Division of Medical Sciences, which carried out the Drug Efficacy Study after passage of the Kefauver-Harris Act.⁶⁰

5. Conclusions

Some past FDA opioid approvals, according to the National Academies, would not meet the standards included in their recommended framework for opioid regulation, a framework that is clearly not yet in place. It is thus inconsistent with the public health approach advocated by the National Academies to continue using the currently inadequate FDA regulatory process for opioid approval and to thereby endanger public health. The ongoing danger of the deficient FDA regulation of opioids provides a strong case for a moratorium on any future opioid approvals until the National Academies-recommended framework is operational. The experts from the National Academies, drawn from within and outside the practice of medicine, made clear that opioids must be considered as a special drug class requiring substantial modifications of the current regulatory process, as reflected in the following statement:

⁵⁹ *Ibid.* pp. 405-409

⁶⁰ *Ibid.* P. 406.

“The committee believes that the preceding chapters of this report establish a scientific and epidemiological basis for special treatment of opioids by the FDA that would involve greater integration of public health considerations at the time of preapproval testing, during regulatory review and approval, and during routine post-approval oversight.”⁶¹

Despite repeated comments from FDA Commissioner Gottlieb that the agency was establishing a framework that endorsed opioids as an exceptional drug class, there is no evidence that this has actually occurred. In accepting the National Academies’ report in July 2017, the Commissioner stated the following:

“I was encouraged to see that many of NASEM’s recommendations for the FDA are in areas where we’ve already made new commitments.

“Among these important new actions is our work to ensure that drug approval and removal decisions are made within a benefit-risk framework that evaluates not only the outcomes of opioids when used as prescribed, but also the public health effects of inappropriate use of these drugs.”⁶²

Likewise, in his November 2, 2018, announcement accompanying the approval of Dsuvia, FDA Commissioner Gottlieb stated the following:

“Given this context, we need to address the question that I believe underlies the criticism raised in advance of this approval: to what extent should we evaluate each opioid solely on its own merits, and how should we also consider, within the broader context of our public health mission including the overall therapeutic armamentarium that we have available for addressing pain, the other opioid analgesics that are already on the market, the epidemic of opioid misuse and abuse that’s gripping our nation and the risk for illicit diversion and abuse?

“I’m committed to considering these key questions as part of a comprehensive process that the FDA has underway to develop a formal benefit and risk framework for how the agency evaluates the safety and efficacy of opioid medicines.”⁶³

However, the promised creation and implementation of the framework recommended by the National Academies has not occurred, and there is no indication that the agency can or will effect the changes necessary in the regulatory process of opioids unless required to do so by the courts, Congress, or the overwhelming ire of the public.

The history of the regulation of opioids by the FDA is a study in failure to act, acting despite contrary evidence, and decision making without due regard to the often predictable, serious

⁶¹ *Ibid.* p. 361.

⁶² Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on National Academies of Sciences, Engineering, and Medicine report on pain management and prescription opioid abuse. July 13, 2017. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm566958.htm>. Accessed March 6, 2019.

⁶³ 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 March 6, 2019.

resulting public health harms attendant to such ill-considered actions. The process of regulating this particular drug class requires specialized knowledge, clinical insight, and a transparent process that too often is foreign to the agency. The failures of the FDA, chronicled in the National Academies' report, have been responsible for the deaths or injuries of many people.

In this petition, we have documented, as examples, the failures of the FDA in the approval process of two opioid formulations: Duvia and reformulated Opana ER. For each of these drugs, we quote the requirements of applicable provisions of the FDCA, describe the failure to comply with these laws, and relate our findings to those in the relevant recommendations in the National Academies' report. Furthermore, we quote previously noted available FDA legal authority to improve opioid regulation, authority which has been denied by the agency for more than five years. We also quote numerous statements made by the Commissioner that give the impression that the process of providing for opioid safety was not within his control or that of the agency.

Since his appointment as the Commissioner of the FDA, Dr. Gottlieb seems to have been making a career of suggesting the need for a new framework for opioid regulation without clear evidence that the agency is any closer to adopting the recommendations laid out by the National Academies' report. In the case of opioid regulation, continued delay will result in the continued loss of life. The President has declared the current opioid crisis a national emergency. We must stand down from the approval of opioids until the regulatory framework envisioned by the National Academies is in place.

C. ENVIRONMENTAL IMPACT

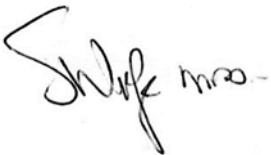
We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

D. ECONOMIC IMPACT

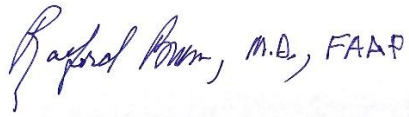
Will be submitted upon request.

E. CERTIFICATIONS

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

A handwritten signature in black ink, appearing to read "Sidney M. Wolfe" with a stylized flourish at the end.

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group

A handwritten signature in blue ink that reads "Raeford Brown, M.D., FAAP". The signature is written in a cursive style.

Raeford E. Brown, Jr, M.D., FAAP
Professor of Anesthesiology and Pediatrics
The University of Kentucky/Kentucky Children's Hospital
Chair, FDA Anesthetic and Analgesic Drug Products Advisory Committee