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**Testimony before the joint FDA Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)**

**Topic: Post marketing requirements studies 3033-1 and 3033-2 on extended release/long-acting opioid analgesic (ER/LA OA) drugs**

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I am Dr. Michael Abrams a senior health researcher with Public Citizen, a nonprofit consumer advocacy organization. Founded in 1971, we currently have 500,000 members and supporters throughout the country.

Our Health Research Group, of which I am a member, uses research and advocacy to address regulatory issues that are the responsibility of the Food and Drug Administration (FDA), including assessing the safety and effectiveness of prescription medications.

I, and Public Citizen overall, have no financial conflicts of interest related to today's meeting.

The Committee is reviewing the results from two post-marketing studies conducted by industry and designed to quantify the incidence of opioid use disorders and overdose events that follow the initiation of long-term opioid analgesic use for medically-supervised non-cancer pain control.<sup>1</sup>

Combined results from both studies also report on various demographic, health care, genetic and other factors that may correlate to use disorder or overdose incidence.

The primary results are summarized in Table 22 of the FDA briefing document. That table shows that among persons initiating long-term use of opioids for non-cancer pain, the 12-month incidence of "abuse" (i.e., intentional, repeated or sporadic use for the purpose of achieving positive psychological or physical effects) was 6 to 9% and the 5-year incidence of moderate to severe Diagnostic Statistical Manual version 5 (DSM-5) opioid use disorder was 3 to 6%. So

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<sup>1</sup> U.S. Food and Drug Administration. FDA briefing document on findings of the completed extended release/long-acting opioid analgesic (ER/LA OA) postmarketing requirements (PMRs) 3033-1 and 3033-2. May 5, 2025. <https://www.fda.gov/media/186254/download>. Accessed May 3, 2025.

called, “pain-adjustment” of the DSM diagnostic criteria yielded 5-year incidence rates of 1 to 3%.

The FDA briefing material notes that these ranges, like those generated before them, are variable, and the more conservative estimates may well miss valid signs of opioid use disorder. In fact, results from these new studies show that substance “misuse” (i.e., intentional, inappropriate use of one’s prescription) is evident in 15 to 23% of opioid initiators within 12-months. Despite complexities in the misuse-to-formal-use-disorder continuum, this high “misuse” estimate marks one of many substantial risks associated with extended opioid use for non-cancer pain. Such high risk of misuse should be quantitatively and prominently stated on all opioid product labels.

Table 22 also shows that the 5-year incidence of an overdose event (including fatalities) ranged from 1 to 4%. These results are consistent with previous estimates according to the FDA reviewers. One concern about the validity of these results is that only 17% of the original study cohort was traceable for the entire 5-year study period.

A curious result also emerged from this analysis: overdose and death rates were apparently highest in the first 3-months of the 5-year follow-up study. FDA reviewers, on p. 96 of their public briefing document, proffer three explanations for this surprising finding: 1) that the first three months of long-term opioid use may be the most intensive period of use, 2) that there may be a “depletion of susceptibles” with time or 3) early titration of the medication may increase unexpected overdose risk. It is concerning that these explanations seem biased towards the notion that risk of overdose is transient and short-lived among those using opioids for chronic non-cancer pain, when we know from much empirical data that increased tolerance, withdrawal and previous overdose events are distinctive risk factors for future events. Accordingly, we encourage the FDA and others to interpret this tenuous finding cautiously. Despite such limitations, these overdose results do reinforce the prospect of major harms associated with long-term opioid use in non-cancer patients. Accordingly, the FDA should require that all opioid product labels clearly, and quantitatively, state these risks for consumers and prescribers.

We agree that the findings for various other factors that appear to influence opioid use disorder and overdose risks are exploratory and underpowered to assess the effects of the many factors considered. Nonetheless, we make the following cautionary observations:

1. Significant effects were observed with gabapentinoid use showing that these seizure medications, widely used off-label for neuropathic pain, correlated with increased risk for opioid use disorder and overdose. Public Citizen has an open petition from 2022 to the Drug Enforcement Agency (DEA) and FDA to schedule gabapentin and gabapentin enacarbil, which currently are unscheduled even as they closely resemble the gabapentinoid pregabalin, a substance that has long been on DEA schedule V.<sup>2</sup>

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<sup>2</sup> Public Citizen. Petition to the DEA and FDA to Classify the Drug Gabapentin as a Schedule V Controlled Substance. <https://www.citizen.org/article/petition-to-the-dea-and-fda-to-classify-the-drug-gabapentin-as-a-schedule-v-controlled-substance/>. February 9, 2022. Accessed May 3, 2025.

2. Formulation, including abuse deterrent formulation, generally does not correlate with either the incidence of opioid use disorder or overdose. These findings support the fact that full opioid agonists are nearly universally associated with a heightened risk of opioid use disorder and overdose. The suggestion, for example, that hydromorphone is more pernicious than other opioids, or that abuse determinant formulations are effective at reducing opioid related morbidity and mortality, are tenuous inferences from these and other data.
3. The three gene-specific burden scores reviewed in these post-marketing studies were not significant correlates of future opioid use disorder. These negative findings are consistent with the limited predictability of genome wide association studies regarding the variance in expression of the opioid use disorder phenotype.<sup>3</sup>

Overall, the two new post-marketing studies are confirmatory of the substantial risks, and a few mediators, associated (or not), with long-term opioid analgesic treatment for non-cancer pain. These studies, however, reveal little new information, and they do not address the overall risks-to-benefits of opioids for pain relief, as such.

Moreover, these post-marketing studies represent an off-the-mark response to a 2012 petition Public Citizen submitted to the FDA— with Physicians for Responsible Opioid Prescribing.<sup>4</sup> That petition requested that the label of all opioid analgesics be changed to unambiguously state that non-cancer pain treatment with such drugs should be limited to the treatment of severe pain, and that dosing should be limited to 100 morphine equivalents or less per day for a maximum period of 90 days.

We believe that our requests from 2012 continue to be appropriate, and the results of these long-overdue post-marketing studies do not eliminate the need for these labeling changes. It is disturbing that the FDA has yet to fully respond to our 2012 petition given that there still is no data showing that long-term use of opioid analgesics for non-cancer pain is overall and in comparison to other therapies, reasonably safe and effective.

Thank you.

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<sup>3</sup> Public Citizen. Letter to the FDA opposing marketing authorization of AvertD for identifying patients at increased genetic risk of opioid use disorder. December 7, 2022. <https://www.citizen.org/article/letter-to-the-fda-opposing-marketing-authorization-of-avertd-for-identify-patients-at-increased-genetic-risk-of-opioid-use-disorder/>. Access May 3, 2025.

<sup>4</sup> Public Citizen. Doctors, researchers and health officials call on FDA to change labels on opioid painkillers to deter misprescribing. July 25, 2012. <https://www.citizen.org/news/doctors-researchers-and-health-officials-call-on-fda-to-change-labels-on-opioid-painkillers-to-deter-misprescribing/>. Accessed May 3, 2025.