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March 14, 2014

The Honorable Joe Manchin
United States Senate
306 Hart Senate Office Building
Washington, DC, 20510

Dear Senator Manchin:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, applauds your recent efforts to (a) overturn the reckless decision by the Food and Drug Administration (FDA) to approve the dangerous, high-dose, non-tamper-resistant opioid drug Zohydro ER; and (b) develop legislation that would target such seriously flawed decision-making by the agency.[1,2]

We also want to call your attention to new disclosures in the media about a tamper-resistant, single-drug hydrocodone product that is in the advanced stages of development. These disclosures further highlight why the FDA's decision to approve Zohydro in October 2013 runs counter to the interests of public health and primarily served to advance the financial interests of Zogenix, the drug's manufacturer. We urge you to investigate why this newly disclosed information failed to sway the FDA against approving Zohydro.

Purdue Pharma, the manufacturer of an FDA-approved tamper-resistant dosage form of oxycodone, announced on March 12 that it has now successfully tested a tamper-resistant form of hydrocodone.[3] The clinical trials for this new investigational form of hydrocodone must have been conducted only after an investigational new drug application was reviewed and approved by the FDA. According to a government website concerning clinical trials, two phase 3 clinical trials testing this tamper-resistant investigational hydrocodone product were initiated in 2011 and

[1] Manchin J. Letter to Secretary of Health and Human Services Kathleen Sebelius. March 10, 2014. http://www.manchin.senate.gov/public/index.cfm/2014/3/manchin-urges-hhs-secretary-to-reverse-approval-of-zohydro. Accessed March 13, 2014.
[2] Devaney T. Manchin takes aim at FDA over approved painkiller. *The Hill*. http://thehill.com/blogs/regwatch/healthcare/200651-manchin-takes-aim-at-fda-over-approved-painkiller. Accessed March 13, 2014.
[3] Dennis B. Maker of Oxycontin developing tamper-resistant hydrocodone drug. *The Washington Post*. March 12, 2014. http://www.washingtonpost.com/national/health-science/maker-of-oxycotin-developing-tamper-resistant-hydrocodone-drug/2014/03/12/85df3dd2-aa0f-11e3-9e82-8064fcd31b5b_story.html. Accessed March 13, 2014.

completed in the late summer of 2013.[4,5] The data from these two studies undoubtedly will provide the primary clinical evidence to be included in a new drug application (NDA) for its tamper-resistant hydrocodone product that Purdue Pharma plans to submit to the FDA in the near future.[6]

Given these revelations regarding the development of Purdue Pharma's product, the FDA's decision to approve Zohydro in October 2013 is even more inexplicable and inexcusable.

Officials in the FDA's Division of Anesthesia and Analgesic Products who were involved in the review and approval of Zohydro almost certainly were aware that Purdue Pharma's tamper-resistant form of hydrocodone was far advanced in the drug development pipeline, when the agency's decision to approve Zohydro was made in October 2013.

Furthermore, the FDA has made statements to the media indicating that the agency was inclined to remove Zohydro from the market once a safer alternative is approved — a clear acknowledgment that Zohydro is less safe than a tamper-resistant formulation would be. For example, following the approval of Zohydro, Dr. Bob Rappaport, director of the Center for Drug Evaluation and Research's Division of Anesthesia and Analgesic Products, reportedly stated, "If and when they, or another manufacturer, are able to create an abuse-deterrent formulation that remains safe and effective for patients, we would certainly give serious consideration to assuring that any non-abuse formulations are removed from the market."[7]

Purdue Pharma has projected that its tamper-resistant form of hydrocodone will be approved by mid-2015, whereas Zogenix, which is also seeking to develop a similar product, does not expect to have its version of the drug available until the end of 2016.[8]

From a public health and clinical standpoint, there is absolutely no need to have a non-tamper-resistant hydrocodone product such as Zohydro on the market between now and 2015, when a tamper-resistant form of the drug is likely to become available. The FDA failed miserably in its primary public health mission by approving Zohydro.

In light of these new revelations, we urge you to initiate an investigation to find out who at the FDA knew about the status of Purdue Pharma's development of a tamper-resistant hydrocodone

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[4] Purdue Pharma LP. Efficacy and safety of hydrocodone bitartrate (HYD) in subjects with moderate to severe chronic low back pain. ClinicalTrials.gov website. NCT01452529. Last verified October 2013. http://www.clinicaltrials.gov/ct2/show/NCT01452529. Accessed March 13, 2014.

[5] Purdue Pharma LP. Long-term safety of once-daily hydrocodone bitartrate (HYD) tablets for moderate to severe chronic nonmalignant and nonneuropathic pain. ClinicalTrials.gov website. NCT01400139. Last verified October 2013. http://www.clinicaltrials.gov/ct2/show/NCT01400139. Accessed March 13, 2014.

[6] Dennis B. Maker of Oxycontin developing tamper-resistant hydrocodone drug. *The Washington Post*. March 12, 2014. http://www.washingtonpost.com/national/health-science/maker-of-oxycotin-developing-tamper-resistant-hydrocodone-drug/2014/03/12/85df3dd2-aa0f-11e3-9e82-8064fcd31b5b_story.html. Accessed March 13, 2014.

[7] Purdue Pharma finds positive phase 3 results of opioid analgesic. *FDA Webview*. March 12, 2014. http://www.fdaweb.com/login.php?sa=v&aid=D5127976&cate=&stid=%241%24Pp1.sb..%24kgceVcvipOjyaf3rjsr7A%2F. Accessed March 13, 2014.

[8] *Ibid*.

product, when they knew it, and why knowledge about this product development did not lead to a decision to reject the NDA for Zohydro. We also urge you to use this new information to bolster your calls for the FDA to withdraw approval of Zohydro, if necessary by passage of your pending legislation. The need for definitive intervention has become more urgent since Zogenix reportedly began shipping Zohydro to pharmacies last week.[9] The interim availability of pure hydrocodone in a non-tamper-resistant dosage form will surely benefit Zogenix until this needlessly dangerous product comes off the market. But this benefit comes at the expense of public health.

Thank you for your attention to this very important matter. We would be happy to meet with you and your staff to answer any questions.

Sincerely,

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[9] Perrone M. Oxycontin maker to offer abuse-resistant Zohydro. *Star Tribune.* http://www.startribune.com/politics/national/249775181.html. Accessed March 13, 2014.