DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

MAR 20 2014

The Honorable Tom Coburn, M.D.
United States Senate
Washington, D.C. 20510-3604

Dear Senator Coburn:

Thank you for your letter of February 12, 2014, cosigned by Senator Mitch McConnell and Senator Lamar Alexander, regarding the approval of Zohydro ER. The Food and Drug Administration (FDA or the Agency) shares your concerns about the abuse and misuse of opioids, including Zohydro ER.

Over the last several years, FDA actively addressed many complex issues associated with the regulation and safe and appropriate use of opioid products, and in particular the class of products to which Zohydro ER belongs, i.e., extended release/long-acting (ER/LA) opioids. In doing so, we are mindful of the need to balance the use of pain medicines by patients who need them to manage their pain, with the need to address the abuse and misuse of prescription opioid medications, which have resulted in many reports of injuries and deaths across the United States. FDA encourages, seeks to incentivize, and, in appropriate cases, requires efforts to address the abuse and misuse of prescription opioid medications.

We have restated your questions below in bold, followed by our responses.

1. **What conditions are in place around the production and distribution of this drug, and how were those conditions evaluated to ensure their effectiveness for preventing misuse, abuse, and diversion?**

   On September 10, 2013, FDA invoked its authority under section 505(o) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require safety labeling changes and post-market studies for all ER/LA prescription opioid analgesics. Zohydro ER is the first drug approved with the new labeling, and the manufacturer of Zohydro will be required to conduct post-market study requirements applicable to ER/LA opioids. The approved labeling includes prominent warnings about abuse, including a boxed warning about the known serious risks of addiction, abuse, and misuse. The labeling also urges prescribers to "assess each patient's risk" before prescribing the drug and to "monitor all patients regularly for the development of [addiction, abuse, and misuse]."

   In addition, Zohydro is a Schedule II controlled substance, and as such, it can only be dispensed through a physician's written prescription, for which no refills are

allowed. There are also stringent recordkeeping, reporting, and physical security requirements for Schedule II controlled substances.

Moreover, Zohydro ER is subject to the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA Opioid Analgesic REMS), which is intended to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse. The ER/LA Opioid Analgesic REMS requires the distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids.

There is no way to completely prevent misuse or abuse of prescription opioid analgesics, even those that have been formulated to have abuse-deterrent features, as such formulations make abuse by certain routes of administration more difficult, but not impossible. While FDA works with companies to facilitate development of novel analgesics that are intrinsically more difficult to abuse or misuse, the greatest tool available to limit these risks is prescriber and patient education. The ER/LA Opioid Analgesic REMS has been designed to provide education to prescribers. Mandatory education about opioids for all DEA registrants would further expand these educational efforts.

2. How does FDA balance patient needs with regard to access to safe and effective pain medication with the potential for abuse, misuse, and diversion?

FDA, together with other Federal agencies, is working to address the large and growing problem of opioid misuse and abuse while seeking to ensure that patients in pain have appropriate access to opioid analgesics. Chronic pain remains a major problem in the United States, and in addition to hearing from those whose lives have been impacted by opioid abuse, at each public meeting, we hear from patients who suffer due to chronic pain and who are desperate for additional options for managing their pain. As cited in the 2011 Institute of Medicine (IOM) report, "Relieving Pain in America," at least 116 million U.S. adults suffer from chronic pain conditions.[1] Also noted in this IOM report (p. 113), "[c]urrently available treatments have limited effectiveness for most people with severe chronic pain." To improve the appropriate use of opioids, FDA has worked to improve the labeling of ER/LA opioid medications to reflect our best understanding of the risks and benefits of these products, including the serious risks associated with addiction, abuse, and misuse. Among other changes, the proposed new labeling for these products clarifies that, because of the risks of addiction, abuse, and misuse, even at recommended doses, and because of the greater risks of overdose and death, these drugs should be reserved for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. Also, as noted in response to Question 1, all ER/LA opioid analgesics are subject to the ER/LA Opioid Analgesics REMS, which is intended to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse.

---

[1] *http://books.nap.edu/openbook.php?record_id=13172&page=R1*

3. **You have previously confirmed that the FDA has the legal authority under the Federal Food, Drug and Cosmetic Act to require drugs, including generic versions, to have an abuse-deterrent formulation. How does the FDA plan to use this authority in regards to approving both brand and generic opiates? Please provide examples of the circumstances in which FDA would use this authority.**

We strongly encourage the development of opioids that can be expected to significantly reduce abuse, and we have recently implemented a policy that provides substantial incentives for sponsors of such products. For example, such products may be eligible for one or more of FDA's expedited review and approval programs, including fast-track designation and priority-review timelines, if the applicable statutory and regulatory criteria are met.

However, we do not believe it is feasible or in the interest of public health at this time to require all opioid products or all ER/LA opioid products to be abuse-deterrent. Rather, we intend to take a case-by-case approach to regulatory decisions concerning the safety and effectiveness of opioid products, in light of the data available to us with respect to each action.

Under FDA's current approach, abuse potential is one aspect of a product's safety that FDA considers, together with all other appropriate factors, in determining whether a product's benefits outweigh its risks. For example, in 2013, FDA announced regulatory decisions related to OxyContin and Opana ER. The sponsors of both products reformulated them with the intention of deterring manipulation for purposes of abuse or misuse. In the case of OxyContin, FDA determined that the original product posed an increased potential for abuse by certain routes of administration compared to the reformulated product. Based on the totality of the data and information available to the Agency, FDA concluded that the benefits of original OxyContin, which lacked abuse-deterrent properties, no longer outweighed its risks, and that original OxyContin was withdrawn from sale for safety or effectiveness reasons. As a result of that decision, FDA will not accept or approve applications for generic versions of the original formulation of OxyContin.

In contrast, for Opana ER, FDA determined that there was insufficient evidence that the original formulation poses an increased risk of abuse compared to reformulated Opana ER. Based on the totality of the data and information available to the Agency, FDA determined that the original formulation's benefits continue to outweigh its risks. FDA therefore concluded that original Opana ER was not withdrawn from sale for safety or effectiveness reasons, and generic versions of the original formulation of Opana ER remain approved.

Consistent with this product-specific approach, FDA approved Zohydro ER after concluding that its benefits outweigh its risks, notwithstanding that the product does not have abuse-deterrent properties.

4. **How does FDA plan to monitor the abuse, misuse, and diversion of pure hydrocodone products, including overdose rates, and evaluate and update the conditions put in place to prevent such abuse, misuse, and diversion if necessary? Please include any plans to work with law enforcement and stakeholders on implementing the most effective strategies to prevent abuse, misuse and diversion, such as the standards for and requirement of abuse deterrent formulations.**

   FDA has created an epidemiology team dedicated specifically to evaluating issues relating to prescription drug abuse. This team has access to data that can monitor drug utilization patterns, which are close to real time in nature.

   There is very limited ability to monitor abuse via spontaneous reports and the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES); however, as the Drug Abuse Warning Network (DAWN) discontinued collecting data after 2011, we really have no substantive manner in which to monitor events relating to drug abuse presenting to emergency departments. We are actively working with the National Center for Health Statistics to determine the feasibility of collecting DAWN-like information from other hospital surveys, and to determine the feasibility of getting drug-specific information from death certificates in which drug involvement was apparent. It is unclear at this point whether either of these efforts will produce useful data. We are also working with Brandeis University to determine whether national data on patterns of drug abuse can be obtained from the state-level Prescription Drug Monitoring Programs (PDMPs). In the meantime, we are relying on sponsors, via their post-marketing study requirements to provide epidemiologic data, noting that it is not real time in nature.

   With regard to the question concerning implementing strategies to prevent abuse and misuse, as mentioned above, FDA has implemented a number of strategies, including the September 2013 ER/LA opioid analgesic safety labeling changes and the institution of post-marketing requirements.

Thank you, again, for contacting FDA concerning this important matter. Please let us know if you have further questions. The same letter has been sent to your cosigners.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation