DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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Re: Docket No. FDA-2013-P-0703

Dear Mr. Barnes, Mr. Cicchon, Ms. Haight, & Ms. Sapp:

This letter responds to your petition (the Petition) asking the Food and Drug Administration (FDA or Agency) to take the following administrative actions to foster a transition to abuse-deterrent opioids and patient access to medication-assisted treatment (MAT) for opioid addiction:

(1) Immediately implement a policy, with limited exceptions, of rejecting new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for opioid drug products in solid oral dosage forms that are not backed by predictive or determinative data supporting the products' potential to reduce abuse.

(2) Acknowledge that the clinical benefits of pharmacotherapies for use in MAT can include patient outcomes other than prolonged abstinence.

(3) Prioritize and expedite additional detailed guidance to industry, on a case-by-case basis or otherwise, on the requirements for assessments of effectiveness and abuse-deterrence.

(Petition at 1, 12). For the reasons explained below, your petition is granted in part and denied in part.

I. BACKGROUND

Abuse and misuse of prescription opioids is a public health epidemic. According to the Centers for Disease Control and Prevention (CDC), sales of prescription opioids in the United States quadrupled from 1999 to 2010.[1] Overdose deaths involving these products increased commensurately over the same period, from 4,030 to 16,651.[2] By 2010 prescription opioids were involved in more than 75 percent of all prescription drug-related overdose deaths.[3]

FDA, together with other Federal agencies, is working to address this large and growing problem while seeking to ensure that patients in pain have appropriate access to opioid analgesics and that individuals addicted to opioids have appropriate access to prescription medications (e.g., methadone) that are used to treat such addiction. In addition to FDA's efforts regarding the development of abuse-deterrent opioids (discussed below), FDA has worked to improve the labeling of 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. On September 10, 2013, FDA invoked its authority under section 505(o) of the Federal Food, Drug & Cosmetic Act (FDCA) to require safety labeling changes and postmarket studies for all extended-release or long-acting (ER/LA) prescription opioid analgesics.[4] 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.

FDA has also worked extensively with the sponsors of ER/LA opioid analgesics to address the risks of addiction, abuse, and misuse through a classwide risk evaluation and mitigation strategy (REMS). The ER/LA opioid analgesics REMS, approved on July 9, 2012, requires sponsors to make training available for health care professionals on proper prescribing practices and to distribute educational materials to prescribers and patients on the safe use of these medications.[5]

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[1] CDC, "Vital Signs: Overdoses of Prescription Opioid Pain Relievers — United States, 1999-2008," Morbidity and Mortality Weekly Report, vol. 60, No. 43 (www.cdc.gov/mmwr/pdf/wk/mm6043.pdf).

[2] CDC, "Opioids drive continued increase in drug overdose deaths," available at http://www.cdc.gov/media/releases/2013/p0220_drug_overdose_deaths.html. See also Jones et al, "Pharmaceutical Overdose Deaths, United States, 2010," Journal of the American Medical Association, vol. 309, no. 7, 657-9.

[3] See footnote 2.

[4] See New Safety Measures Announced for Extended-release and Long-acting Opioids, available at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm363722.htm.

[5] See ER/LA Opioid Analgesic REMS, available at http://www.er-la-opioidrems.com/IwgUI/rems/home.action.

A. Abuse-Deterrent Opioids

FDA considers the development of opioid analgesics with abuse-deterrent properties to be a public health priority, and supports that priority in several ways. First, 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.[6]

FDA has also consulted with advisory committees in connection with the development, evaluation, and labeling of abuse-deterrent opioids. For instance, in September 2009 FDA convened joint meetings of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss Purdue's new formulation of OxyContin (oxycodone hydrochloride) Controlled-Release Tablets as well as Acura Pharmaceuticals, Inc.'s NDA for a product containing oxycodone hydrochloride and niacin.[7] Another joint meeting of these committees was held in October 2010 to discuss, among other things, how sponsors should design and conduct postmarket epidemiological or observational studies to evaluate whether and to what extent products designed to reduce the likelihood and incidence of abuse actually do so.[8]

Next, FDA has published two draft guidances relevant to the development of abuse-deterrent formulations of controlled prescription drugs. *Abuse-Deterrent Opioids – Evaluation and Labeling* describes FDA's recommendations regarding the data that should be provided to demonstrate that a formulation has abuse-deterrent properties, how those data will be evaluated by the Agency, and what labeling claims may be approved based on the data.[9] *Assessment of*

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[6] See draft guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics* (June 2013), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

[7] Summary meeting minutes of the September 24, 2009, joint meeting concerning reformulated OxyContin are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187629.pdf. Summary meeting minutes of the April 22, 2010, joint meeting concerning Acurox are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220274.pdf.

[8] Summary meeting minutes are available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM236242.pdf. The products at issue were Embeda (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules and reformulated OxyContin, but the knowledge gained and expertise developed in connection with those products should help facilitate the development and evaluation of other potentially abuse-deterrent opioid formulations.

[9] See the draft guidance for industry, *Abuse-Deterrent Opioids - Evaluation and Labeling* (Jan. 2013) (Abuse-Deterrent Opioids draft guidance), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. This draft guidance was produced following mandates in the White House prescription drug abuse plan, *Epidemic: Responding to America's Prescription Drug Abuse Crisis* (2011), available at http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf and the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. Law 112-144 (section 1122(c)).

Abuse Potential of Drugs discusses, among other things, the design and implementation of clinical studies that may be used to help assess whether a proposed abuse-deterrent formulation can be expected to reduce a product's abuse potential relative to an appropriate comparator product.[10]

Finally, FDA has recently made regulatory decisions regarding the reformulations of two opioid drug products, OxyContin (oxycodone hydrochloride) Controlled-Release Tablets and Opana ER (oxymorphone hydrochloride) Extended-Release Tablets, which are discussed in Part II.A of this response.

B. Medication-Assisted Treatment for Opioid Addiction

MAT refers to any treatment for opioid addiction that includes a medication (e.g., methadone, buprenorphine, levo-alpha acetyl methadol, naltrexone) approved for treatment of opioid addiction detoxification or maintenance treatment.[11] As you note in your petition, the Office of National Drug Control Policy (ONDCP) supports the development of new medications to treat addiction, the implementation of MAT protocols, and the expansion of MAT utilization within the criminal justice system.[12] FDA has approved several products for use in the treatment of opioid addiction or opioid dependence.

II. DISCUSSION

A. FDA's Current Policy On Abuse-Deterrent Opioids

You ask that FDA reject NDAs and ANDAs for opioid drug products in solid oral dosage forms that are not backed by predictive or determinative data supporting the products' potential to deter abuse, except where FDA finds that the proposed medication prevents or alleviates a drug shortage or otherwise addresses a significant unmet public health need in a special needs population (Petition at 1, 7-8, 12, and footnote 1). We interpret your request to mean that all NDAs and ANDAs would have to be shown to have abuse-deterrent properties as a condition of approval (unless your proposed drug shortage exception or unmet public health need exception applies).[13]

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[10] See the draft guidance for industry *Assessment of Abuse Potential of Drugs* (Jan. 2010) at pages 8-9, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

[11] Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration, Medication-Assisted Treatment for Opioid Addiction in Opioid, Chapter 1. Introduction, available at http://www.ncbi.nlm.nih.gov/books/NBK64168/.

[12] See National Drug Control Strategy, Office of National Drug Control Policy (2013), at pages 1, 2, & 22, available at http://www.whitehouse.gov//sites/default/files/ondcp/policy-and-research/ndcs_2013.pdf.

[13] While you refer to "abuse-deterrent" and "non-abuse-deterrent" formulations throughout your Petition, you do not define the evidentiary threshold you believe FDA should use.

We are very concerned about the epidemic of prescription opioid abuse and are working to address it in many ways, as discussed in Part I.A of this response. We also 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.[14] However, we do not believe your proposed approval requirement for this class of drugs is currently feasible or appropriate.

As discussed in the Abuse-Deterrent Opioids draft guidance, the science of abuse deterrence technology is in its early stages. Both the drug and formulation technologies involved and the clinical, epidemiological, and statistical methods for evaluating those technologies are still rapidly evolving. FDA published the draft guidance nine months ago and continues to actively work with potential sponsors interested in developing abuse-deterrent opioid products. To date, we have approved labeling characterizing a product's expected impact on abuse (as contemplated in the draft guidance) for just one product, reformulated OxyContin.

Abuse-deterrent technologies have important limitations. For example, the available data indicate — and therefore the labeling for reformulated OxyContin states — that the product is *expected* to make abuse via injection difficult, and is *expected* to reduce abuse via the intranasal route. The data are not yet sufficiently mature to confirm these expectations. Reformulated OxyContin also is not intended or believed to have any impact on the most common form of abuse of this and many other prescription opioids — swallowing intact tablets or capsules.

Accordingly, while FDA strongly supports a transition to abuse-deterrent opioids, we do not believe it is feasible or in the interest of public health at this time to require all products in the class to be abuse-deterrent (even subject to the exceptions you propose). In light of the need for further data and scientific development in this nascent and rapidly evolving area, FDA intends to continue to take a product-by-product approach to regulatory decisions concerning the safety and effectiveness of opioid products. As the science of abuse deterrent technologies continues to develop, we will continue to evaluate our approach to regulatory decisions concerning these products.

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, FDA recently 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

[14] If a sponsor provides sufficient evidence that its opioid drug product has significant abuse-deterrent properties, FDA will approve labeling information concerning those properties.

OxyContin was withdrawn from sale for safety or effectiveness reasons.[15] As a result of that decision, FDA will not accept or approve applications for generic versions of the original formulation of OxyContin.[16]

In contrast, for Opana ER, FDA determined that there is 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 and marketed.[17]

Consistent with this product-specific approach, today FDA approved Zohydro ER (hydrocodone bitartrate) Extended-Release Capsules after concluding that its benefits outweigh its risks, notwithstanding that the product does not have abuse-deterrent properties. The data show that Zohydro ER is safe and effective for the treatment of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The approved labeling includes prominent warnings about abuse, including a boxed warning about the known serious risks of addiction, abuse, and misuse (among others). 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]." Zohydro ER is subject to the ER/LA Opioid Analgesics REMS, which is intended to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse. The 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.[18]

Furthermore, Zohydro ER is the first approved single-entity hydrocodone product and the first extended-release product containing hydrocodone. Having an additional safe and effective option for ER/LA opioid treatment is important for several reasons. First, individual patients respond differently to different opioids. A patient may experience better pain management and/or more tolerable adverse effects with one opioid compared to another. Second, the benefits of opioids can wane as a patient becomes opioid-tolerant. A common clinical practice strategy to address these issues is to rotate the patient from one opioid to another.[19] Also, prescribers will

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[15] See Determination that the OXYCONTIN (Oxycodone Hydrochloride) Drug Products Covered by New Drug Application 20-553 Were Withdrawn From Sale for Reasons of Safety or Effectiveness, 78 Fed. Reg. 23,273 (April 18, 2013).

[16] See *FDA approves abuse-deterrent labeling for reformulated OxyContin*, available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm348252.htm.

[17] See Letter Response from Dr. Janet Woodcock to Endo Pharmaceuticals, Inc., FDA-2012-P-0895 (May 10, 2013).

[18] Like other ER/LA opioids, Zohydro ER is subject to control under Schedule II of the Controlled Substances Act. 21 U.S.C. 801 et seq.; 21 CFR 1308.12. Schedule II control reflects a finding that the drug has a "high potential for abuse" and that abuse "may lead to severe psychological or physical dependence." Schedule II drugs are subject to certain requirements and restrictions pursuant to the Controlled Substances Act.

[19] For example, in a retrospective review of 273 patients, 106 were rotated through at least one other opioid. The reasons given for the rotation included lack of adequate analgesia (43%) and intolerable side effects (20%) or both (15%). Kloke, M. et al. Toxicity and/or insufficient analgesia by opioid therapy: risk factors and the impact of

now have the option of moving a patient who is responding well to an immediate-release hydrocodone combination product but who would benefit from treatment with an extended-release formulation to Zohydro ER, obviating the need to switch the patient to a different active ingredient with an extended-release formulation.[20] Next, because Zohydro ER is a single-entity product, prescribers may titrate Zohydro ER for individual patients without the limitations or toxicity concerns associated with the non-opioid active ingredient (e.g., acetaminophen) present in all other approved hydrocodone products.[21] Finally, there are no approved hydrocodone products (single-entity or combination) with abuse-deterrent properties.

For all of these reasons, FDA has determined that Zohydro ER's benefits outweigh its risks.

You state that the continued approval of non-abuse-deterrent opioid products would have a variety of negative effects, including: (a) expending limited FDA resources to review such applications, (b) increasing the supply of relatively low-cost drugs that people are willing and able to abuse, with attendant negative public health outcomes, (c) undercutting efforts to shift the market from more easily abused traditional opioids to less readily abused medications with abuse-deterrent features, (d) compromising the monitoring and analysis of the epidemiological benefits of new abuse-deterrent products, and (e) disincentivizing investment in the research and development to bring innovative abuse-deterrent products to market (Petition at 7-8). We have considered the potential consequences of our current case-by-case approach and your proposed across-the-board approach. We believe our current approach provides sufficient incentives for the development of abuse-deterrent drug products while preserving access to a range of therapeutic agents for patients in pain. While no approach to this complex issue is without trade-offs and potentially negative consequences, we believe that the case-by-case approach we have adopted is appropriate and warranted at this time for the reasons discussed above.

Accordingly, FDA intends to continue to assess the benefit-risk profile of each opioid drug product, including its risk of abuse, on a case-by-case basis. This approach is intended to balance the public health interest in the development of drug products with abuse-deterrent properties with the need to preserve access to a range of therapeutic agents (both brand-name and generic) for patients in pain. We therefore deny your request to reject all applications for opioid drug products in solid oral dosage forms that are not backed by predictive or determinative data supporting the products' potential to deter abuse.

B. Benefits of Medication-Assisted Treatment of Opioid Addiction

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changing the opioid. A retrospective analysis of 273 patients observed at a single center. Support Care Cancer (2000): 8:479-486. The practice of opioid rotation for long-term management of patients in pain is included in the treatment guidelines published by the American Pain Society and the American Academy of Pain Medicine. Chou, R., et al. Opioid Treatment Guidelines. The Journal of Pain (2009) 10:113-130.

[20] The patient may not respond as well to a different active ingredient. Furthermore, switching opioids requires titrating the patient to a new dose, because the patient can be expected to respond differently to the same amount of a different opioid.

[21] Unbundling the acetaminophen from the opioid has been suggested as a means of reducing liver injury associated with acetaminophen toxicity related to use of opioid-acetaminophen combination products. Lee, W. Acetaminophen toxicity: changing perceptions on a medical/social issue. Hepatology (2007): 46: 966-970.

You state that in May 2013 FDA "withheld approval" of an NDA for a buprenorphine implant to be indicated for use in MAT of opioid addiction even though the majority of the members of the Psychopharmacology Drugs Advisory Committee voted for approval (Petition at 6). You note that, in connection with its review, FDA stated that "even after allowing four months for engagement in treatment, only three [buprenorphine implant]-treated patients were fully abstinent from opioids" (Petition at 6-7). Although you appear to advocate the approval of this buprenorphine implant product, you have not requested that we take any specific action related to the application. Accordingly, we decline to further discuss this application in this response.[22]

You also contend that studies show that MAT can lead to substantial benefits aside from abstinence such as retention in treatment, reduction in illicit substance use, improved psychiatric status, greater social adjustment, and increase in functional state and quality of life, and other benefits (Petition at 9). You therefore request that FDA acknowledge in writing that the clinical benefits of pharmacotherapies for use in MAT can include patient outcomes other than prolonged abstinence (Petition at 1 and 12). You claim that "a failure to acknowledge the wide array of potential clinical benefits of MAT" will disincentivize or retard the development of transition to abuse-deterrent opioid medications (Petition at 11).

FDA agrees that MAT for opioid addiction can yield a number of benefits other than prolonged abstinence. While abstinence from drug use or significant reductions in drug use are common clinical endpoints used to assess proposed MAT products, they are not the only health and psychosocial benefits that can accrue to patients who are successfully treated, whether with MAT or another treatment.

Clinical trial endpoints are not intended to capture all of the potential benefits of using a particular treatment. In focusing on drug-use behavior (whether abstinence or other degrees of reduction in use) as an outcome measure for clinical trials, FDA does not intend to convey that a particular intervention has or could have no other meaningful beneficial effects. We have accepted studies that use drug-use behavior as an endpoint because it may be impractical to demonstrate other potential clinical benefits in the context of a time-limited clinical trial. However, we would be open to considering studies designed to directly measure improved psychiatric status, greater social adjustment, increase in functional state, or other direct measures of how the patient feels or functions, assuming the measurement instruments and methods were appropriate and the relevance of the chosen outcomes were adequately supported by data.

C. Additional Guidance Regarding Abuse-Deterrent Opioids and MAT of Opioid Addiction

You ask that FDA provide additional detailed guidance to industry, on a case-by-case basis or otherwise, on its expectations for assessments of purportedly abuse-deterrent opioid products

[22] The proposed product you discuss is the subject of a pending NDA, the existence of which has been previously publicly disclosed. With exceptions not relevant here, FDA regulations prohibit the disclosure of data or information contained in such an NDA before sending an approval letter (see 21 CFR 314.430(d)(1)). See also 5 U.S.C. 552(b)(4); 18 U.S.C. 1905; 21 U.S.C. 331(j); 21 CFR 20.61.

(Petition at 12). You also appear to ask FDA to provide additional guidance, on a case-by-case basis or otherwise, regarding how effectiveness may be established for opioid products intended for use in MAT for opioid addiction (Petition at 12).

FDA is committed to finalizing the Abuse-Deterrent Opioids draft guidance following our review of comments from stakeholders and other interested persons. Although FDA is not able to comment on any other specific guidance documents at this time, we plan to continue to follow our Good Guidance Practices (GGPs), which detail the circumstances under which FDA should issue guidance documents and the procedures governing such issuance (21 CFR 10.115).

Furthermore, FDA will continue to engage with and provide advice to individual applicants using our regular procedures, including written correspondence and Agency-applicant meetings.

Accordingly, to the extent your request encompasses the commitments detailed above, it is granted. To the extent your request includes other action or actions, it is denied.

III. CONCLUSION

As explained above, the Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research