



## DEPARTMENT OF HEALTH & HUMAN SERVICES

SEP 23 2014

Food and Drug Administration  
10903 New Hampshire Avenue  
Building #51  
Silver Spring, MD 20993

Frederick S. Mayer, R.Ph., M.P.H.  
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101 Lucas Valley Road, Suite 384  
San Rafael, CA 94903

Re: Docket No. FDA-2013-P-1606

Dear Mr. Mayer:

This letter responds to your petition dated November 25, 2013 (Petition). In the Petition, you ask the Food and Drug Administration (FDA) to take several related actions with respect to hydrocodone-containing products listed in schedule II of the Controlled Substances Act.<sup>1</sup> We interpret your Petition to request that FDA:

1. require that hydrocodone-containing products, be formulated to deter abuse;
2. adopt through regulation certain “standards of practice and corresponding responsibilities” for the dispensing of prescriptions for schedule II hydrocodone-containing products; and
3. hold a public hearing and open a docket to receive comments from the public regarding your request that FDA require that all schedule II hydrocodone-containing products be formulated to deter abuse and regarding your request that FDA adopt certain standards of practice and corresponding responsibilities for the dispensing of prescriptions for schedule II hydrocodone-containing products.

We have carefully considered your Petition. For the reasons set forth below, your Petition is granted in part and denied in part.

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<sup>1</sup> In your petition, you include certain broad statements regarding schedule II drugs more generally. For example, you state that “no schedule II drug be allowed, either brand or generic, before the abuse-deterrent technology is implemented into the product before FDA approval” (see Petition at 3). However, your particular requests are limited to hydrocodone-containing schedule II products (see Petition at 1). Accordingly, we interpret your request to be limited to hydrocodone-containing schedule II opioid products.

## I. BACKGROUND

### A. FDA's Efforts to Address Opioid Abuse and Misuse

The abuse and misuse of opioid medications has become a public health crisis. Opioid-involved drug overdose death rates in the United States have increased 4-fold from 1999 to 2008.<sup>2</sup> Emergency department visits, substance abuse treatment admissions, and economic costs associated with opioid abuse have also increased dramatically over the same period.<sup>3</sup> This rise in adverse events has largely paralleled the rise in the number of prescriptions for these products.<sup>4</sup>

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. In addition to FDA's efforts regarding the development of opioid medications with abuse-deterrent properties (discussed in section I.B below), FDA has worked to improve the labeling of opioid medications to reflect our best understanding of the benefits and risks 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, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)) to require safety labeling changes and postmarket studies for all extended-release or long-acting (ER/LA) prescription opioid analgesics.<sup>5</sup> The new labeling for this class of products was approved on April 16, 2014.<sup>6</sup> Among other changes, the labeling 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 class-wide risk evaluation and mitigation strategy

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<sup>2</sup> [Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research](http://www.iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx), Institute of Medicine Report, available at <http://www.iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx>.

<sup>3</sup> [Vital signs: overdoses of prescription opioid pain relievers — United States, 1999 – 2008](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm), Centers for Disease Control and Prevention, available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm>.

<sup>4</sup> Id.

<sup>5</sup> See New Safety Measures Announced for Extended-release and Long-acting Opioids, available at <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm363722.htm>.

<sup>6</sup> With the exception of Zohydro ER, which was approved with the new class labeling on October 25, 2013. See <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm369273.htm>.

(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.<sup>7</sup>

FDA also recently announced the establishment of a docket to receive suggestions, recommendations, and comments on innovative packaging, storage, and disposal systems — technologies or designs — that could be used to prevent or deter abuse of opioid analgesics.<sup>8</sup>

Finally, FDA, through the Department of Health and Human Services (HHS), has recommended to the Drug Enforcement Administration (DEA) that hydrocodone combination products should be reclassified from schedule III to schedule II, a more restrictive schedule.<sup>9</sup> Based in part on this recommendation, DEA has issued a final rule to reschedule hydrocodone combination products to schedule II, effective October 6, 2014.<sup>10</sup>

## B. FDA's Efforts to Encourage Abuse-Deterrent Formulations

FDA considers the development of opioid medications with abuse-deterrent properties to be a public health priority and supports that priority in several ways. First, these 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.<sup>11</sup>

FDA has also consulted with advisory committees in connection with the development, evaluation, and labeling of opioids with abuse-deterrent properties, and has held an advisory committee meeting 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.<sup>12</sup>

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<sup>7</sup> See ER/LA Opioid Analgesic REMS, available at <http://www.er-la-opioidrems.com/lwgUI/remis/home.action>.

<sup>8</sup> In the *Federal Register* of April 9, 2014 (79 FR 19619), FDA published a notice entitled “Center for Drug Evaluation and Research; Use of Innovative Packaging, Storage, and/or Disposal Systems to Address the Misuse and Abuse of Opioid Analgesics; Request for Comments; Establishment of a Public Docket.” See also “Center for Drug Evaluation and Research; Use of Innovative Packaging, Storage, and/or Disposal Systems to Address the Misuse and Abuse of Opioid Analgesics; Reopening of the Comment Period” (79 FR 38541, July 8, 2014).

<sup>9</sup> See Statement on Proposed Hydrocodone Reclassification from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, available at <http://www.fda.gov/Drugs/DrugSafety/ucm372089.htm>.

<sup>10</sup> See Final Rule “Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products From Schedule III to Schedule II” (79 FR 49661, August 22, 2014).

<sup>11</sup> See FDA's guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

<sup>12</sup> See the summary meeting minutes of the September 24, 2009, joint meeting concerning reformulated OxyContin, available at

Next, FDA has published two draft guidances relevant to the development of abuse-deterrent formulations. The draft guidance *Abuse-Deterrent Opioids —Evaluation and Labeling* describes FDA's current thinking regarding the data that should be provided to demonstrate that a formulation has potentially abuse-deterrent properties, how those data will be evaluated by the agency, and what labeling claims may be approved based on the data.<sup>13</sup> FDA participated in the Abuse-Deterrence Formulation Science meeting held on September 30 and October 1, 2013, which provided a forum to discuss the draft guidance. FDA is committed to publishing a final version of this guidance as soon as possible. The draft guidance *Assessment of Abuse Potential of Drugs* discusses, among other things, the design and implementation of clinical studies that should be used to help assess whether a drug that is a new molecular entity has abuse potential and includes a discussion on approaches to assess proposed abuse-deterrent formulations of the drug.<sup>14</sup>

Additionally, FDA is conducting and supporting research on opioid formulations designed to deter abuse. This includes development of in vitro testing methodologies to assess purportedly abuse-deterrent opioid formulations.

FDA has also made regulatory decisions regarding opioid drug products reformulated with the intent of making those products more difficult to manipulate for purposes of abuse.<sup>15</sup>

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<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187629.pdf>. See also the summary meeting minutes of the April 22, 2010, joint meeting concerning Acurox, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM220274.pdf>. In addition, see the summary meeting minutes of the October 21-22, 2010, meeting concerning OxyContin, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM236242.pdf>.

<sup>13</sup> See the draft guidance for industry *Abuse-Deterrent Opioids - Evaluation and Labeling* (January 2013) (Abuse-Deterrent Opioids draft guidance), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf>. This draft guidance, when finalized, will represent FDA's current thinking on this topic. The 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](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), Public Law 112-144 (section 1122(c)).

<sup>14</sup> 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>. This draft guidance, when finalized, will represent FDA's current thinking on this topic.

<sup>15</sup> See FDA's "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 FR 23273, April 18, 2013); see also Letter Response from Dr. Janet Woodcock to Endo Pharmaceuticals, Inc., regarding Opana ER, FDA-2012-P-0895 (May 10, 2013).

Today, FDA is publishing a *Federal Register* notice announcing that it is opening a docket and holding a public meeting on October 30 and 31, 2014, to obtain public input on issues related to opioids, including opioids with abuse-deterrent properties. The public meeting will focus on scientific and technical issues related to the development and in vitro assessment of abuse-deterrent formulations of opioid medications. In addition, the meeting will focus on FDA's approach to assessing the benefits and risks of opioids, including opioids with abuse-deterrent properties, FDA's relevant actions to date, and how FDA can continue to and further support advances in this field.

## II. DISCUSSION

### A. Request That All Schedule II Opioid Products Have Abuse-Deterrent Properties

In the Petition, you ask FDA to take several related actions with respect to hydrocodone-containing products listed in schedule II of the Controlled Substances Act. We interpret these related requests as a request that FDA require that all schedule II opioid products, and in particular all such products containing hydrocodone, be formulated to deter abuse.<sup>16</sup>

We are very concerned about the epidemic of prescription opioid abuse and are working to address it in many ways, as discussed in section I.A of this response. We also strongly encourage the development of opioids that can be expected to significantly reduce abuse, as discussed in section I.B. However, as we said in response to a similar request from the Center for Lawful Access and Abuse Deterrence (CLAAD) and several other groups, we do not believe that requiring abuse-deterrent technologies for all opioid drug products is currently feasible or appropriate.<sup>17</sup>

As explained in the CLAAD petition response:

[T]he 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.<sup>18</sup>

To date, there are only two products —Targiniq and reformulated OxyContin — for which FDA has approved labeling regarding their abuse-deterrent properties consistent with Abuse-Deterrent Opioids draft guidance. Also, currently available abuse-deterrent technologies have significant limitations. As noted in the CLAAD petition response:

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<sup>16</sup> See footnote 1.

<sup>17</sup> See Letter Response from Dr. Janet Woodcock to CLAAD, the National Association of Drug Diversion Investigators, Ryan's Cause, and National Family Partnership, FDA-2013-P-0703 (October 25, 2013) (CLAAD petition response).

<sup>18</sup> See footnote 17 at 5.

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.<sup>19</sup>

Accordingly, we concluded as follows:

[W]hile 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.<sup>20</sup>

We reach the same conclusion regarding your request that all hydrocodone-containing schedule II drugs, be formulated to deter abuse (Petition at 3). That is, we decline to impose such a requirement at this time, but will continue to make regulatory decisions concerning the safety and effectiveness of all schedule II opioid drug products, including those containing hydrocodone, on a product-by-product basis.

## B. Standards of Practice for Pharmacists Dispensing Schedule II Drugs

You also request that FDA implement “a standard of practice (SOP) for prescription monitoring programs” that will set forth “responsibilities for pharmacists” dispensing schedule II hydrocodone-containing drugs (Petition at 1). We interpret your request to mean that FDA should require that pharmacists dispensing schedule II hydrocodone-containing drugs follow certain standards of practice.<sup>21</sup>

In accordance with section 505-1 of the FD&C Act, FDA has the authority to require a REMS when measures beyond the FDA-approved labeling are needed to ensure that the drug’s benefits outweigh its risks. A REMS can consist of a number of different elements. For example, if certain criteria are met, FDA can require that health care providers who prescribe a drug have

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<sup>19</sup> Id.

<sup>20</sup> Id.

<sup>21</sup> Your Petition states that five sample standards of practice were included as attachments to your Petition (Petition at 3), but it appears that no such attachments were included.

particular training or experience, and that pharmacies or practitioners that dispense a drug are specially certified. See section 505-1(f).

As discussed above, in July 2012, FDA required a REMS for ER/LA opioid analgesics that is focused on prescriber education and is intended to reduce the potential for serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while ensuring that patients with legitimate need for these drugs continue to have access to them. The sponsors of ER/LA opioid analgesic products are required to submit periodic assessments of the REMS to FDA. FDA carefully reviews the assessments, and uses the results to determine whether changes are needed. We decline to adopt your request that FDA require pharmacists dispensing schedule II hydrocodone-containing drugs follow certain standards of practice.

Accordingly, this request is denied.

### **C. Public Meeting and Open Public Comment**

In addition, you request that FDA hold “public hearings and open up a Federal Registry [sic] to establish standards to add drug-abuse deterrent technology to all hydrocodone schedule II products and to implement standards of practice and corresponding responsibilities for pharmacists” (Petition at 3). We interpret your request to mean that FDA should open a docket to receive comments from the public regarding your request that FDA (1) require all schedule II hydrocodone-containing products to be formulated to deter abuse and (2) adopt through regulation certain standards of practice for the dispensing of schedule II drugs.

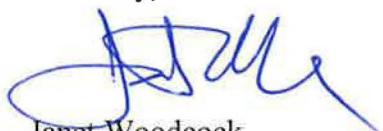
As noted previously, today FDA published a *Federal Register* notice announcing a public meeting on October 30, and 31, 2014, and opening a docket to obtain input on issues related to abuse-deterrent formulations of opioid medications. At the public meeting, FDA will address, among other topics, the idea that at some point — after abuse-deterrent formulations have become available for a number of different opioid active moieties and after we have obtained more experience with this field — FDA may determine that the risks of all or most opioid products that lack abuse-deterrent properties outweigh the benefits in light of available therapies. We will discuss whether, under such circumstances, it would be appropriate to impose a class-based abuse-deterrent formulation requirement on certain classes or sub-classes of opioid products. We believe this satisfies your request for a meeting and opportunity for comment regarding the notion that all schedule II hydrocodone-containing products must be formulated to deter abuse. Accordingly, this aspect of your request is granted.

Establishing standards of practice for the dispensing of schedule II drugs through regulation, however, is outside the scope of this meeting and docket, and FDA has no plans to hold a public meeting or open a docket on this topic at this time. Accordingly, this aspect of your request is denied.

**III. CONCLUSION**

After careful consideration, and in light of the foregoing, your Petition is granted in part and denied in part.

Sincerely,



Janet Woodcock  
Director  
Center for Drug Evaluation and Research