DEPARTMENT OF HEALTH & HUMAN SERVICES

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

SEP 10 2013

Andrew Kolodny, MD
President, Physicians for Responsible Opioid Prescribing
920 48th Street, Suite 1510
Brooklyn, NY 11219

Re: Docket No. FDA-2012-P-0818

Dear Dr. Kolodny:

This letter responds to the citizen petition submitted by Physicians for Responsible Opioid Prescribing (PROP), which was received by FDA on July 26, 2012 (Petition). The Petition describes PROP's concerns about the safety and efficacy of opioid analgesic drugs for long-term use in chronic non-cancer pain, and requests that the Food and Drug Administration (FDA or Agency): (1) "[s]trike the term 'moderate' from the indication [of opioid analgesics] for non-cancer pain"; (2) "[a]dd a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain"; and (3) "[a]dd a maximum duration of 90-days for continuous [daily] use" for non-cancer pain (Petition at 2).[1]

FDA has carefully reviewed PROP's Petition and the numerous comments submitted to the public dockets[2] by government entities, medical societies, healthcare providers, patients, and other members of the public. For the reasons described in detail in this response, the Petition is granted in part and denied in part.

Today, on the basis of the information discussed below, FDA has notified application holders for extended-release/long-acting (ER/LA) opioid analgesics that, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(o)(4)), important safety labeling changes are needed to the labeling of ER/LA opioid analgesics.[3] It is the agency's intent that these changes, which are described more fully below, will help more effectively communicate the serious risks of misuse, abuse, neonatal opioid withdrawal syndrome (NOWS), addiction, overdose, and death associated with the use of ER/LA opioids overall, and during pregnancy. FDA has also determined that more data are needed about the safety of long-term use of opioids. Pursuant to section 505(o)(3) of the FD&C Act, FDA is therefore requiring all new drug application (NDA) sponsors of ER/LA opioids to conduct postapproval studies and clinical trials

[1] The Petition requests pertain to analgesia products; therefore, this response is limited to opioids with indications for analgesia.

[2] FDA received comments on the PROP citizen petition in the above-captioned docket and comments relevant to the PROP citizen petition in the docket for a part 15 hearing the agency held in February 2013, titled Impact of Approved Drug Labeling on Chronic Opioid Therapy (Part 15 Hearing) (*see* Docket No. FDA-2012-N-1172).

[3] Pursuant to section 505(o)(4) of the FD&C Act, FDA is notifying holders of approved NDAs and holders of approved ANDAs that reference a NDA that is not currently marketed.

(post-marketing requirements, or PMRs) to assess certain known serious risks of ER/LA opioid use: misuse, abuse, hyperalgesia, addiction, overdose, and death.

I. BACKGROUND

A. Opioids

Opioids are a class of powerful pain-relieving agents that includes oxycodone, hydrocodone, and morphine, among others. When prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority.[4] Chronic pain is a serious and growing public health problem: it "affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence."[5] There is also evidence that pain is inadequately treated in many patients.[6] However, pain is a self-reported symptom that is difficult to quantify, and its treatment is complex.

Opioids also have grave risks, the most well-known of which include addiction, overdose, and even death. The labeling for these products contains prominent warnings about these risks. Moreover, the boxed warning states that all patients should be "routinely monitor[ed]...for signs of misuse, abuse, and addiction." Even proper use of opioids under medical supervision can result in life-threatening respiratory depression, coma, and death (see Boxed Warning and Section 5.3 of Warnings in current labeling). Indeed, a Centers for Disease Control and Prevention (CDC) analysis published in February 2013 documents an 11th straight year of increases in drug overdose deaths, with opioids being involved in 75% of pharmaceutical overdose deaths, either alone or in combination with other drugs.[7]

Most opioid-only drugs are controlled under Schedule II of the Controlled Substances Act.[8] By law, prescriptions for Schedule II drugs cannot be refilled; patients need a new prescription to obtain the drug beyond the initial number of doses prescribed.[9] There are also strict recordkeeping, reporting, and physical security requirements. This level of

---

[4] *See* "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." Committee on Advancing Pain Research, Care, and Education; Institute of Medicine. 2011:1-364 (available at http://www.nap.edu/catalog.php?record_id=13172).

[5] *Id.* at p. 5.

[6] *Id.* at p. 1.

[7] Jones CM, Mack, KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013; 309(7): 657-9.

[8] *See* 21 U.S.C. 801 *et seq*; 21 CFR 1308.12. There are some opioids in Schedule III (*e.g.*, buprenorphine, *see* 21 CFR 1308.13(e)(2)(i)) and Schedule IV (*e.g.*, butorphanol and pentazocine, *see* 21 CFR 1308.14(f)). Tramadol, a synthetic opioid, is not currently scheduled under the Controlled Substances Act, *see* www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf.

[9] Although opioid drug labeling does not recommend a limit on the number of doses a patient should receive, the Schedule II status of most opioid drugs imposes certain restrictions on their availability. 21 CFR 1306.12(a). However, prescribers "may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a Schedule II controlled substance" as long as certain conditions are met. 21 CFR 1306.12(b)(1).

control reflects a finding that most opioid drugs have "high potential for abuse" and that "[a]buse of the drug . . . may lead to severe psychological or physical dependence."[10]

Opioid drugs have been approved for different conditions of use based on the data and information submitted by the sponsor of each drug product. Accordingly, product labeling may vary among approved opioid drugs, and such drugs may be prescribed to different patient populations.[11] The approved indications for ER/LA opioid analgesics are uniform, however. These drugs are currently indicated "for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[12] The current labeling for these drugs also contains a prominent statement that they are **not** for use:

- As an as-needed (prn) analgesic,
- For pain that is mild or not expected to persist for an extended period of time,
- For acute pain,
- In the immediate postoperative period, or
- For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.[13]

The labeling for some ER/LA opioid analgesics also states that they are for use (or for use at higher doses) only in opioid-tolerant patients.[14]

---

[10] 21 U.S.C. 812(b)(2).

[11] For example, indications for which particular IR opioid products have been approved include "the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate" (Oxecta (oxycodone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/202080s001lbl.pdf); "the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate" (Codeine sulfate (NDA 022402) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022402s006lbl.pdf); and "the management of pain in patients where an opioid analgesic is appropriate" (Dilaudid (hydromorphone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2007/019892s015lbl.pdf).

[12] OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[13] Labeling for OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf (internal references omitted).

[14] *See, e.g.,* labeling for Exalgo (hydromorphone hydrochloride) (NDA 021217) and Duragesic (fentanyl) (NDA 019813). Further, certain opioid drugs also have limitations of use on the higher doses, with labeling stating that higher doses are for opioid-tolerant patients only. *See, e.g.,* labeling for Avinza (morphine sulfate) extended-release capsules (NDA 021260), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/021260s017lbl.pdf and OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

B. ER/LA Opioid Analgesic Risk Evaluation and Mitigation Strategy

FDA approved a shared-system Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics on July 9, 2012 (ER/LA Opioid Analgesic REMS).[15] The goal of the ER/LA Opioid Analgesic REMS is to "reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of [ER/LA opioids] while maintaining patient access to pain medications."[16] Under the REMS, "[a]dverse outcomes of concern include addiction, unintentional overdose, and death."[17] The REMS is currently limited to ER/LA opioid products because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids.[18]

Currently, more than 30 products are subject to the ER/LA Opioid Analgesic REMS.[19] The ER/LA Opioid Analgesic REMS contains requirements for 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. Prescriber education training is considered ER/LA Opioid Analgesic REMS-compliant if, among other things, it includes the elements described in the "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (FDA Blueprint).[20] The FDA Blueprint provides guidance to prescribers to enable appropriate ER/LA opioid prescribing practices, as well as information prescribers can use in counseling patients about the risks and benefits of ER/LA opioid use.

C. Public Input

FDA has received a considerable amount of input from stakeholders and other commenters on issues pertaining to the benefits and risks of opioid use. For example, FDA participated in a two-day workshop in May 2012 hosted at the National Institutes of Health (NIH), called, "Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop."[21] Several stakeholders and other members of the public gave presentations

---

[15] *See* www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf (most recently modified in April, 2013).

[16] *Id.* at p. 2.

[17] *Id.*

[18] *See* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q5; *see also, e.g.*, Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf) (providing data showing growing harm associated with ER/LA opioids).

[19] The list of drugs required to have a REMS, grouped by application holder, may be found at www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf.

[20] Available at http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf.

[21] *See* Docket No. FDA-2012-N-0067; *see also* http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm.

about issues relating to opioid treatment of chronic pain, and additional comments and subsequent input were posted to the public docket for that meeting.[22]

On February 7 and 8, 2013, FDA held a public hearing on chronic use of opioid drug products, titled, "Impact of Approved Drug Labeling on Chronic Opioid Therapy" (Part 15 Hearing).[23] FDA requested information, particularly scientific evidence, on issues pertaining to the use of opioid drugs in the treatment of chronic pain, including diagnosis and understanding of pain, understanding and adhering to the labeling of pain-treating products, and limiting opioid prescriptions and use.[24] The Agency received input from dozens of presenters, including patients, individuals who had lost loved ones due to opioids, clinicians, public health experts, professional associations, academicians, and others, including PROP. FDA also received over 600 comments to the Part 15 Hearing docket. The majority were from patients voicing concerns that labeling changes could make legitimate patient access to opioid analgesics more difficult.[25] The remainder reflected the same diversity of viewpoints and concerns presented during the hearing itself.

FDA also received more than 1900 comments on the PROP Petition. Many public health agencies and organizations supported the requests in the Petition, citing concerns about increased opioid use and abuse.[26] However, the majority of comments opposed PROP's requests. Many professional societies (*e.g.*, the American Academy of Pain Medicine, the American Medical Association, the American Society of Anesthesiologists, the American Pain Society) did not support the Petition and stated that the data cited by PROP did not support PROP's requests (particularly those requests for limits on dose and duration of use of opioids). Professional societies also expressed concern that the labeling changes requested by PROP were not supported by scientific evidence, and that a "one-size-fits-all" approach to a maximum dose or duration of treatment would be problematic and inconsistent with the need for individualized treatment and the variability among patient responses to opioids.[27]

---

[22] *See* Docket No. FDA-2012-N-0067.

[23] *See* Docket No. FDA-2012-N-1172.

[24] *See* www.gpo.gov/fdsys/pkg/FR-2012-12-19/pdf/2012-30516.pdf.

[25] However, for privacy reasons, many comments from individual patients are not publicly available on www.regulations.gov. They nevertheless are considered to be included in the public docket.

[26] *See, e.g.*, comments from the New York City Department of Health and Mental Hygiene (Docket No. FDA-2012-P-0818-0785); County of Los Angeles Public Health (Docket No. FDA-2012-P-0818-0336); Denver Public Health (Docket No. FDA-2012-P-0818-0677); and the National Center on Addiction and Substance Abuse at Columbia University (Docket No. FDA-2012-P-0818-0691).

[27] *See, e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165); the American Medical Association (Docket No. FDA-2012-P-0818-0783); the American Society of Anesthesiologists (Docket No. FDA-2012-P-0818-0246); the American Pain Society (Docket No. FDA-2012-P-0818-0187); the American Academy of Physical Medicine and Rehabilitation (Docket No. FDA-2012-P-0818-0658); the American Society of Regional Analgesia and Pain Medicine (Docket No. FDA-2012-P-0818-0276); the Texas Pain Society (Docket No. FDA-2012-P-0818-0331); and the Florida Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0333). Some commenters submitted critiques of PROP's cited studies that identified the studies' limitations. *See, e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165). For example, the Florida Academy of Pain Medicine states, "it appears that the petitioners are asking for changes to the indications for long-term

II. SAFETY LABELING CHANGES

After evaluating stakeholder and commenter input regarding opioid labeling, and based on FDA's review of relevant literature, FDA has determined that safety labeling changes to the labeling of ER/LA opioid analgesics are needed to more effectively communicate to prescribers the serious risks associated with these drugs, and to more clearly describe the population in whom these drugs should be used in light of these serious risks—thus encouraging better prescribing, monitoring, and patient counseling practices involving these drugs. FDA is therefore exercising its authority under section 505(o)(4) of the FD&C Act to notify application holders that modifications to ER/LA opioid analgesic labeling are needed.[28] It is the agency's intent that these changes will help reduce inappropriate prescribing[29] and help curb the increase in misuse, abuse, NOWS, addiction, overdose, and death associated with ER/LA opioid analgesic use.

These safety labeling changes apply only to ER/LA opioid analgesics, and, at present, FDA is not requesting or requiring that any labeling changes be made to IR opioids or opioid/non-opioid combination products (which include both an IR opioid and a non-opioid analgesic).[30] Much of the literature FDA reviewed assessed opioid use from all opioid sources, or did not necessarily separate data according to opioid formulation (*i.e.*, ER/LA versus IR or opioid/non-opioid combinations). However, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products; indeed, the recognition of

---

high-dose opioid therapy (LTHDOT) for non-cancer pain, based on a small number of studies with significant methodological shortcomings and findings that are not conclusive. In short, they are basing their request for label changes on the same kind of evidence they themselves, criticize as being insufficient to support the safety and efficacy of LTHDOT for non-cancer pain" (Docket No. FDA-2012-P-0818-0333).

[28] Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FD&C Act, as codified in section 505(o)(4) of the FD&C Act, to authorize FDA to require holders of approved drug applications to make safety labeling changes (SLCs) if the agency becomes aware of "new safety information" that FDA determines should be included in the labeling of the drug. *New safety information* is information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug of which the Agency has become aware (that may be based on a new analysis of existing information) since the drug was approved, the REMS was approved, or since the last assessment of the approved REMS; or the effectiveness of the approved REMS for the drug obtained since the last assessment of such strategy. *See* section 505-1(b)(3) of the FD&C Act.

[29] Pain patients in the United States receive care from prescribers with different backgrounds and levels of experience and expertise in treating pain. IMS Health, Vector One®: National (VONA). Data Extracted September 2012. Weblink: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM337148.pdf. For example, some prescribers may not understand how to identify patients at risk for addiction, how to identify behaviors associated with misuse and abuse, and how to manage patients who are receiving opioids for chronic pain so as to reduce the risks of misuse, abuse, NOWS, addiction, overdose and death.

[30] Therefore, the agency denies PROP's Petition insofar as it requests labeling changes for IR opioids, or opioid/non-opioid combination products.

disproportionate safety concerns for ER/LA opioids informed FDA's decision to require the ER/LA Opioid Analgesic REMS. For example, data show that the risk for misuse and abuse is greater for ER/LA opioids.[31] Because they are intended to release the drug over a longer period of time, many ER/LA opioids contain higher doses of opioids compared to IR opioids or opioid/non-opioid combinations. This increases the risk of a fatal outcome in the event of an overdose, and may make ER/LA opioids more desirable in the eyes of opioid abusers and addicts. Furthermore, ER/LA opioids are often used in a chronic pain setting. Thus, in light of the risks posed by ER/LA opioids, and the totality of available data on both ER/LA opioids specifically and opioid drugs in general, the Agency has decided to make ER/LA opioid analgesics its current focus.

First, FDA is requiring changes to the boxed warning for ER/LA opioid analgesics to give greater emphasis and prominence to the risks of misuse, abuse, NOWS, addiction, overdose, and death. For example, the first sentence of the new boxed warning provides that ER/LA opioids "expose patients and other users to the risks of opioid addiction, abuse, and misuse which can lead to overdose and death." The new boxed warning also urges prescribers to "assess each patient's risk" before prescribing, and to "monitor all patients regularly for the development of these behaviors or conditions."

Second, FDA is requiring changes to the Indications and Usage section of the labeling. As noted above, ER/LA opioid analgesics currently are "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[32] The Agency has concluded that use of terminology predicated only on a categorical "severity scale" (e.g., mild, moderate, severe) to characterize the intensity of pain for which ER/LA opioids are indicated does not sufficiently focus prescribers' attention on their responsibility to make an individualized assessment of patient needs in light of the serious risks of ER/LA opioids. Given these serious risks, especially those of overdose and death, the Agency believes that clarity as to the appropriate use of such drugs is of the utmost importance. The new language clearly communicates to prescribers that ER/LA opioid analgesics should be used only when alternative treatments are inadequate because of the serious risks of these drugs. The new language also identifies specific examples of alternative treatment options, namely, "non-opioid analgesics or immediate-release opioids," and provides additional guidance on when such treatments may be deemed inadequate to provide sufficient management of pain.

Furthermore, the new labeling language underscores that patients in pain should be assessed not only by their rating on a categorical pain intensity scale, but also based on a

---

[31] Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf).

[32] *See, e.g.*, OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

more thoughtful determination that their pain — however it may be defined — is *severe enough* to require daily, around-the-clock, long-term opioid treatment, *and* for which alternative treatment options are inadequate. This framework better enables prescribers to make decisions based on a patient's individual needs, given the serious risks associated with ER/LA opioids, against a backdrop of alternatives such as IR opioids and non-opioid analgesics. It allows prescribers to make an assessment of pain relative to a patient's ability to perform daily activities or enjoy a reasonable quality of life, not only on where a patient's pain falls on an intensity scale, and assess if ER/LA opioids are needed after determining whether (a) the pain is severe enough to require daily, around-the-clock, long-term opioid treatment, and (b) if alternatives to ER/LA opioids are inadequate to manage such pain, in light of the serious risks associated with ER/LA opioid analgesics.

The revised indication language reads as follows:

> **"[Tradename] is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.**
>
> **<u>Limitations of Use</u>**
> **• Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] 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.**
> **• [Tradename] is not indicated as an as-needed (prn) analgesic."**

This new language is intended to prompt prescribers to more closely assess each individual patient's condition, and carefully evaluate whether alternative treatment options such as non-opioid analgesics or IR opioids are appropriate. The new language is intended to reflect that ER/LA opioid analgesics should be prescribed only when the prescriber determines that such alternatives are ineffective, not tolerated, or would otherwise be inadequate.

Third, FDA is notifying application holders of the need for changes to the Dosage and Administration, Warnings and Precautions, Drug Interactions, and Use in Specific Populations sections of ER/LA opioid analgesic labeling. These changes are specifically intended to urge prescribers to weigh carefully whether the benefits of an ER/LA opioid outweigh its serious risks on a patient-by-patient basis. If an ER/LA opioid analgesic is prescribed, the labeling changes emphasize that prescribers should monitor patients carefully for signs of abuse and addiction. FDA is also notifying application holders of the need for changes to the Patient Counseling Information and the product-specific Medication Guides to improve the communication of risks to patients.[33] The Agency

[33] Following the approval of the safety labeling changes, a REMS modification will be required to incorporate the approved safety labeling changes into the REMS materials, as applicable.

believes that the changes will improve communication of serious risks associated with the use of these products and help improve the safe use of ER/LA opioid analgesics overall.

FDA intends these changes to enable not only a more careful and thorough approach to determining whether ER/LA opioid analgesics should be prescribed for a particular patient, but also allows prescribers to better assess whether the serious risks associated with ER/LA opioids, including the risks of misuse, abuse, addiction, overdose and death associated with ER/LA formulations, are offset by the benefits ER/LA opioids may provide in managing pain for an individual patient.

Accordingly, PROP's request that FDA remove the term "moderate" from the indication for ER/LA opioid analgesic drugs is granted for the reasons explained above. As explained above, the changes to the labeling also reflect a departure from an indication based solely on a severity scale, and transitions to an indication that facilitates careful prescribing decisions based on an individualized assessment of a patient's situation (*i.e.*, whether an individual's pain is severe enough to require daily, around-the-clock, long-term opioid treatment) and a heightened recognition that, because of the serious risks associated with the use of these drugs, ER/LA opioids should be used only when alternative treatment options are inadequate.[34]

All of PROP's labeling change requests are limited to "non-cancer" pain, a distinction that is not made in current ER/LA opioid analgesic labeling. It is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer, and comments to the Petition docket reflect similar concerns.[35] FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling.[36]

In accordance with section 505(o)(4) of the FD&C Act, the ER/LA opioid analgesic application holders are required to submit by October 10, 2013, a supplement proposing changes to the approved labeling to reflect the new safety information, or else notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted.[37]

---

[34] When other analgesics are contraindicated or ineffective, restricting the indication of opioid drugs to treatment of severe pain only could leave some patients with chronic pain with an impaired ability to carry out daily activities, resulting in a diminished quality of life. *See* National Pharmaceutical Council (2001): Pain: Current Understanding of Assessment, Management, and Treatments, http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_related_research/pub_quality_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf.

[35] *See, e.g.*, comments from National Hospice and Palliative Care Organization (Docket No. FDA-2012-P-0678); Purdue Pharma (Docket No. FDA-2012-P-0818-0707).

[36] FDA notes that some epidemiology studies make distinctions between cancer and non cancer pain. However, while such classifications may be standard in epidemiological research, FDA believes that they are not relevant to ER/LA opioid labeling.

[37] *See* section 505(o)(4)(B) of the FD&C Act.