DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAR 2 2 2016

RE: Docket No. FDA-2014-P-0205

Dear Mr. Mathers and Ms. Davidson:

This letter responds to your citizen petition, docket number FDA-2014-P-0205,[1] and the supplement to the petition (dated June 17, 2015), submitted on behalf of Purdue Pharma L.P. (Petitioner or Purdue), in which you request that the Food and Drug Administration (FDA or Agency):

1. Promptly exercise its authority under Section 505(o) of the Federal Food, Drug, and Cosmetic Act to seek and, if necessary, impose safety labeling changes on immediate-release opioid analgesics[2] that parallel the final safety labeling changes resulting from completion of the 505(o) procedures initiated on September 10, 2013 for extended-release and long-acting opioid analgesics.[3]
2. Assure that the indications for use and other safety labeling information for immediate-release and extended-release and long-acting opioid analgesics convey the same warnings and precautions regarding the risks of opioid use and misuse.

[1] In preparing this response, the Agency also considered the comments submitted to the public docket.

[2] The Petition does not define the term "immediate-release opioid analgesic." FDA interprets this term to refer to immediate-release formulation (i.e., not sustained-release, controlled-release, extended-release, or long-acting formulation) drugs indicated for analgesia, one or more of whose active ingredients agonize the mu-opioid receptors in the brain. Because non-extended-release formulations of certain naturally long-acting opioids (e.g., methadone) were required to change their labeling along with extended-release formulations of other opioids, FDA assumes that Petitioner means the term "immediate release opioid analgesic" to exclude non-extended-release formulations of naturally long-acting opioids.

[3] On September 10, 2013, FDA notified holders of approved new drug applications (NDAs), and holders of approved abbreviated new drug applications (ANDAs) that reference a non-marketed NDA drug, of extended-release and long-acting (ER/LA) opioid drugs indicated for analgesia that it was requiring certain safety-related labeling changes pursuant to its authority under section 505(o)(4) of the FD&C Act. For further information, please see the letter to ER/LA opioid analgesic NDA and certain ANDA holders, available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf. These labeling changes were approved on April 16, 2014. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM393455.pdf.

(Petition at 2). We have carefully considered your petition and supplement (hereinafter Petition), and, for the reasons that follow, your Petition is granted in part,[4] albeit on grounds other than those advanced by Petitioner.

Today, on the basis of the information discussed below, FDA has notified application holders for immediate-release (IR) opioid analgesics that, under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(o)(4)), safety labeling changes (SLCs) are needed for IR opioid analgesics.[5] The purpose of these changes, which are described below, is twofold. First, to more effectively communicate the serious risks of misuse, abuse, neonatal opioid withdrawal syndrome (NOWS), addiction, overdose, and death associated with the use of IR opioids.[6] Second, to more clearly describe the population in which IR opioids should be used in light of these serious risks – thus encouraging better prescribing, monitoring, and patient counseling practices involving these drugs. These SLCs are similar, but not identical, to the extended-release and long-acting (ER/LA) opioid analgesic SLCs approved in 2014.

I. BACKGROUND

A. Opioid Analgesics

Opioids are a class of powerful pain-relieving agents that include oxycodone, hydrocodone, and morphine, among others. Opioids can help effectively manage pain and alleviate suffering when other alternative pain medicines have not been or are not expected to provide enough pain relief. The pain-relieving properties of opioids clearly serve a public health need,[7] and there is evidence that pain is inadequately treated in many patients.[8] However, pain is a self-reported symptom that is difficult to quantify, and its treatment is complex. Opioids also have grave risks, including addiction, overdose, and death. Thus, these drugs must be prescribed and used carefully to ensure that their benefits outweigh their risks in the patient populations who need to use them.

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[4] The Petition is granted because most of the IR opioid analgesic SLCs will, indeed, "parallel" those the ER/LA opioid analgesic SLCs. However, to the extent that certain aspects of the ER/LA opioid analgesic labels will not apply to IR opioid analgesics (e.g., certain limitations of use), or will not convey "the same warnings and precautions regarding the risks of opioid use and misuse, and to the extent that Petitioner asks FDA to base IR opioid SLC changes on the data and arguments provided in the Petition, those aspects of the Petition are denied.

[5] Under section 505(o)(4) of the FD&C Act, FDA has notified holders of approved NDAs, and holders of approved ANDAs that reference an NDA that is not currently marketed.

[6] FDA is also requiring changes regarding: serotonin syndrome with concomitant use of serotonergic drugs; adrenal insufficiency; androgen deficiency; and anaphylaxis, angioedema, and other hypersensitivity reactions.

[7] 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).

[8] Id. at p. 1.

Opioids are available, broadly speaking, as either ER/LA or IR products.[9] Some opioids in the ER/LA category are naturally long acting; others are incorporated into extended release formulations. To provide adequate opioid release over a longer period of time, ER opioid formulations often include strengths that overlap those of, and exceed the highest strength available as an IR product. (For example, OxyContin (oxycodone hydrochloride), an ER/LA opioid analgesic, is marketed in strengths from 10 milligrams (mg) to 80 mg oxycodone per tablet, in contrast to IR oxycodone, which is marketed in strengths from 10 mg to 30 mg per tablet.) The greater amount of active ingredient in many ER opioids increases the risks associated with unintentional and intentional overdose, and the extended-release mechanism or long-acting nature of ER/LA opioids means that an individual who overdoses at any dosage level is in danger from the risks of overdose (e.g., depressed breathing rate) for a longer period of time. However, an overdose of either type of opioid formulation, ER/LA or IR, can result in serious outcomes, including death.

Opioid drugs have been approved for different conditions of use based on the data and information submitted by the sponsor of each drug product, and based on the Agency's thinking at the time of drug approval. Accordingly, product labeling varies among approved opioid drugs, and these drugs are indicated for different patient populations. Although ER/LA opioid analgesic labeling was standardized in the April 14, 2014 finalization of FDA's class-wide SLC requirements, the labeling for IR opioid analgesics is more varied, including their indications. 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[,]"[10] "the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate[,]"[11] and "the management of pain in patients where an opioid analgesic is appropriate[.]"[12] In practice, IR opioid analgesics are used in a variety of situations: acute pain, chronic pain, post-operative pain (including after dental surgery), and "as-needed" pain relief for intermittent pain or intermittently debilitating pain (e.g., osteoarthritis pain that occasionally rises to the level of requiring opioid analgesia).

B. Relevant Authority

1. Statutes

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[9] Long-acting opioid analgesics, such as methadone, have a longer period of action because of the inherent characteristics of the drug substance rather than because of the drug's formulation. Long-acting opioids can generally be dosed at once- or twice-a-day dosing intervals without the need for a separate extended-release formulation.

[10] Oxaydo (oxycodone hydrochloride) labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202080s002lbl.pdf (note that "Oxaydo" previously was called "Oxecta").

[11] Codeine sulfate (NDA 022402) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022402s006lbl.pdf.

[12] Dilaudid (hydromorphone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2007/019892s015lbl.pdf.

Section 505(o)(4) of the FD&C Act[13] authorizes FDA to require holders of approved applications for prescription drug products to make SLCs if the Agency becomes aware of new safety information that FDA believes should be included in the labeling of the drug. *New safety information* is defined in part as:

> Information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the postmarket 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 risk or an unexpected serious risk associated with use of the drug that the [Agency] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since [a] risk evaluation and mitigation strategy (REMS) [for the drug] was approved, or since the last assessment of the approved REMS.[14]

Once the Agency notifies application holders of the new safety information and labeling changes, those application holders must respond within 30 days: either by submitting a supplement proposing changes to the approved labeling to reflect the new safety information, or by notifying the Agency that they do not believe a labeling change is warranted and submitting a statement detailing the reasons why such a change is not warranted.[15] The Agency and the application holders may enter into discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information, at the conclusion of which FDA may issue an order requiring the SLCs to be made.[16]

2. Regulations and Guidances

Section 201.56 of title 21, Code of Federal Regulations, sets forth the general requirements on content and format of labeling for human prescription drug products, including that the labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug.[17] Section 201.57 contains the general format[18] and requirements[19] for such labeling sections as the "Boxed Warning," "Indications and Usage," "Dosage and Administration," "Warnings and Precautions," and "Use in Special Populations" sections of labeling. For example, the "Warnings and Precautions" section "must describe [among other things,] clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the

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[13] See also guidance for industry: *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

[14] See section 505-1(b)(3) of the FD&C Act (21 U.S.C. 355-1(b)(3)).

[15] Section 505(o)(4)(B) of the FD&C Act.

[16] Section 505(o)(4)(D)-(E) of the FD&C Act.

[17] 21 CFR 201.56(a)(1).

[18] 21 CFR 201.57(a)(4); 21 CFR 201.57(a)(6); 21 CFR 201.57(a)(7); 21 CFR 210.57(a)(10); 21 CFR 210.57(a)(13).

[19] 21 CFR 201.57(c)(1)-(c)(3); 21 CFR 201.57 (c)(6); 201 57(c)(9).

drug)."[20] However, "[c]ertain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box."[21] FDA has provided guidance on the risks that should be included in the "Warnings and Precautions" and boxed warning sections of labeling in the guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*.[22]

II. FDA ACTION: IR OPIOID ANALGESIC SAFETY LABELING CHANGES

FDA is deeply concerned about the growing epidemic of opioid abuse, dependence and overdose in the United States. In an effort to reduce the resulting substantial public health burdens, and based on the new safety information discussed above, the Agency has decided to require sweeping safety labeling changes for IR opioid analgesics – many of which currently have labeling that is decades old. These labeling changes are needed to fulfill the same goals as the recent ER/LA opioid analgesic SLCs: 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. Thus, FDA is exercising its authority under section 505(o)(4) of the FD&C Act to notify application holders that modifications to IR opioid analgesic labeling are needed. The Agency's intent is that these changes will help curb misuse, abuse, NOWS, addiction, overdose, and death associated with IR opioid analgesic use. Given the frequency with which IR opioids are prescribed, we hope that the impact of these labeling changes will ease the public health burden associated with the negative effects of these drugs.

A. New Safety Information

IR opioid abuse and the resulting consequences pose a serious and ongoing threat to public health. Recent studies by Cassidy et al.[23] and Johnson et al.[24] suggest that IR opioid abuse has continued to occur at a considerable level in recent years despite efforts to mitigate abuse of these drugs, such as implementation of prescription drug monitoring programs (PDMPs), insurer drug utilization reviews, and law enforcement efforts to close "pill mills." The Cassidy observational study examined the prevalence of abuse in a sample of individuals assessed for substance abuse problems in treatment centers and other sites across the United States from 2008-2011. Over the 4-year study period, the proportion of assessments in which the individual reported IR opioid abuse in the 30 days prior to the start of treatment remained

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[20] 21 CFR 201.57(c)(6).

[21] 21 CFR 201.57(c)(1).

[22] Available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf.

[23] Cassidy TA, DasMahaptra P, Black RA et al. (2014) Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. Pain Medicine, 15: 440-451.

[24] Johnson H, Paulozzi L, Porucznik C et al. Decline in drug overdose deaths after state policy changes – Florida, 2010-2012. Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 63 (26), Published July 4, 2014: 569-574.

relatively constant, ranging from 12.15% to 14.08% throughout the study period[25] – a level that is too high from the perspective of public health.

The Johnson study viewed the impact of IR opioid risks through a different lens, examining Florida medical examiner data regarding deaths due to opioids from 2003-2012. During the time when hydrocodone was only available in an IR formulation, hydrocodone-related overdose deaths steadily increased from 2003-2010, ranging from 1.1 per 100,000 population to 1.7 per 100,000 population – although from 2010-2012, hydrocodone-related overdose deaths decreased to 1.3 per 100,000 population. When hydromorphone was only available in IR formulation (from 2006-2009), hydromorphone-related overdose deaths remained steady, from 0.2-0.3 per 100,000 population.[26] These data suggest that IR opioid products continue to be associated with overdose deaths at a level that has a considerable negative impact on the public health.

The Cassidy and Johnson studies directly document that the use of IR opioid analgesics is associated with the existence and persistence of abuse, overdose, and death. These three risks do not exist in isolation, however. Abuse can give rise to addiction and vice versa; for example, the Cassidy study on abuse includes a cohort of individuals where many are already in treatment for addiction, thus illustrating the linkage between the two risks. And in many cases, overdose and death are the result of misuse and abuse.[27] Given the interrelated nature of these opioid risks (misuse, abuse, addiction, overdose, and death), the Cassidy and Johnson studies support an understanding that the risks of misuse and addiction continue to occur at high levels, and continue to contribute to the significant public health burdens associated with IR opioid analgesic use.

In addition, a study by Patrick et al.[28] found that a clinically significant proportion of pregnant women dispensed IR opioids had children who were diagnosed with neonatal abstinence syndrome (NAS)[29] at birth. The primary objective of this retrospective, longitudinal cohort study was to identify neonatal complications associated with prescription opioid exposure during pregnancy, and to determine whether predictors could be established to identify infants at risk for developing NAS. Prescription, vital records, hospital, and outpatient claims data

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[25] See Cassidy TA, DasMahaptra P, Black RA et al. (2014) Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. Pain Medicine, 15: 440-451.

[26] See Johnson H, Paulozzi L, Porucznik C et al. Decline in drug overdose deaths after state policy changes – Florida, 2010-2012. Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, 63 (26), Published July 4, 2014: 569-574.

[27] We note that there is not yet a generally accepted definition of "misuse," although one purpose of the ER/LA opioid analgesic post-marketing studies FDA required in September 2013 (see September 10, 2013 Letter to ER/LA Opioid Analgesic NDA Holders (available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf)) is to facilitate the creation of such a definition. Thus, some studies may use the terms "abuse" and "misuse" interchangeably.

[28] Patrick SW, Dudley, J, Martin PR et al. (2015) Prescription opioid epidemic and infant outcomes. Pediatrics, 135 (5): 842-850.

[29] FDA uses the term *NOWS* to refer to NAS caused by withdrawal from opioid drugs, legal or illegal.

were collected on mothers and infants enrolled in the Tennessee Medicaid program between 2009 and 2011. In this study, the likelihood of an NAS diagnosis was found to increase with more recent (30 days prior to birth) and longer (a week or longer supply) IR opioid exposure periods,[30] thus underscoring the risks of NAS resulting from IR opioid use during pregnancy.

These data and data analyses satisfy the statutory standard for *new safety information* as, among other things, "information derived from . . . peer-reviewed biomedical literature. . . or other scientific data deemed appropriate by the [Agency]" about the "serious risk[s]" associated with the use of IR opioid analgesics.[31] This new safety information, taken together, demonstrates that IR opioid products are associated with a substantial risk for misuse, abuse, NOWS, addiction, overdose and death.

B. IR Opioid Analgesic Safety Labeling Changes

Accordingly, FDA is notifying application holders regarding the need to add or amend[32] a boxed warning in the labeling for IR opioid analgesics to give greater emphasis and prominence to the risks of misuse, abuse, NOWS, addiction, overdose, and death.[33] For example, the new boxed warning provides that IR 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 "[a]ssess each patient's risk" before prescribing, and to "monitor all patients regularly for the development of these behaviors or conditions." Regarding the risks of NOWS, the new boxed warning states: "Prolonged use of [PRODUCT NAME] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, [*(for non-parenteral drugs)* advise the patient of the risk of neonatal opioid withdrawal syndrome and] ensure that appropriate treatment will be available."

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[30] In addition, the authors found that IR opioids were dispensed to pregnant women with a much higher frequency than any other opioid.

[31] See section 505-1(b)(3) of the FD&C Act.

[32] Certain IR opioid analgesics already have boxed warnings for discrete issues, such as the risk of medication errors for IR opioid analgesic oral solutions (see, e.g., labeling information for oxycodone hydrochloride oral solution (NDA 200535), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200535s009lbl.pdf), or risks associated with non-ER/LA fentanyl products (see, e.g., labeling information for Abstral (fentanyl citrate) (NDA 022510), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022510s013lbl.pdf; labeling information for Ionsys (fentanyl citrate) (NDA 021338), available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021338s005lbl.pdf).

[33] Misuse, abuse, NOWS, addiction, overdose and death constitute serious adverse reactions because, among other things, they may result in death, inpatient hospitalization or prolongation of inpatient hospitalization, or significant incapacity (see section 505-1(b)(4)-(b)(5) of the FD&C Act; 21 CFR 201.57(c)(1); see also Guidance for Industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf)).

Second, FDA is requiring changes to the Indications and Usage section of the labeling.[34] As noted above, IR opioid analgesics currently have a variety of indications based on the diversity of the products and the clinical data submitted in support of the individual marketing applications. Given the serious risks associated with IR opioids, the Agency believes that greater clarity as to the appropriate use of these drugs is of the utmost importance. The new language more clearly communicates to prescribers that, because of the serious risks associated with these drug products, IR opioid analgesics should be used only when alternatives have not been or are not expected to be tolerated, or have not provided or are not expected to provide adequate analgesia. The new language also identifies specific examples of alternative treatment options, namely, "opioid/non-opioid combination products" or "non-opioid analgesics."

The required indication for the IR opioid analgesics will parallel but not exactly duplicate the language from the ER/LA opioid analgesic indication and may be modified to fit the individual product, as appropriate. The revised indication language reads as follows:

[TRADENAME] is indicated for the management of [*insert product-specific indication*] pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.X)]*, reserve [TRADENAME] for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products (as appropriate)]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

Third, FDA is notifying application holders of the need for changes to the Dosage and Administration,[35] Warnings and Precautions, [36] Drug Interactions,[37] and Use in Specific Populations[38] sections of IR opioid analgesic labeling. These changes are specifically intended to urge prescribers to carefully weigh whether the benefits of an IR opioid outweigh its serious risks on a patient-by-patient basis. If an IR opioid analgesic is prescribed, the labeling changes emphasize that prescribers should carefully monitor patients for signs of abuse and addiction. The Agency believes that the changes will improve communication of serious risks associated with the use of these products and help improve the safe use of IR opioid analgesics overall.

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[34] See 21 CFR 201.57(c)(2).

[35] See 21 CFR 201.57(c)(3).

[36] Because misuse, abuse, NOWS, addiction, overdose and death are serious adverse reactions, they should be included in the Warnings and Precautions section of labeling (see 21 CFR 201.57(c)(6)).

[37] See 21 CFR 201.57(c)(8).

[38] See 21 CFR 201.57(c)(9).

FDA intends these changes to prompt prescribers to more carefully and thoroughly evaluate whether IR opioid analgesics should be prescribed for a particular patient, and to help prescribers better assess whether the serious risks associated with IR opioids, including the risks of misuse, abuse, NOWS, addiction, overdose and death, are offset by the benefits IR opioids may provide in managing pain for an individual patient.

In accordance with section 505(o)(4) of the FD&C Act, the IR opioid analgesic application holders are required to submit by April 21, 2016, 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.[39] If the IR opioid application holders do not submit the requested SLCs, or if FDA disagrees with alternative language that the application holders propose, the FD&C Act provides timelines under section 505(o)(4) for discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety information.[40] At the conclusion of these discussions, section 505(o)(4)(E) authorizes FDA to issue an order directing application holders to make labeling changes as appropriate.

III. PETITIONER'S ARGUMENTS REGARDING RELATIVE RISKS OF OPIOID ANALGESICS

Petitioner argues that the IR opioid analgesics are associated with "the same potential adverse consequences as ER/LA opioid analgesics, including the… risks of abuse, misuse, and overdose…" and that, therefore, these risks should be presented in the labeling for IR opioid analgesics "in a similar fashion" (Petition at 2). Petitioner presents its arguments in two ways: (1) by using data from several sources -- MarketScan (an administrative claims database), the National Poison Data System, the NAVIPPRO Addiction Severity Index – Multimedia Version substance-use-disorder treatment network, and IMS Health's LRx database -- to support its conclusion that IR opioid analgesics have the same risks "with comparable or higher incidence" than ER/LA opioid analgesics; and (2) by criticizing FDA's determination, noted in both the ER/LA opioid analgesic REMS and the ER/LA opioid analgesic SLCs, that ER/LA opioid analgesics have disproportionate risks.

The Agency does not agree with Petitioner's data analyses. FDA has concluded that the described studies are fundamentally deficient and cannot adequately address whether ER/LA opioid analgesics and IR opioid analgesics have similar abuse profiles. Further, the Agency's conclusion remains that ER/LA opioid analgesics, as a class of drugs, present disproportionate risks to users: many ER/LA opioid analgesic drugs contain more active ingredient than IR analgesics on a per-tablet basis, and the long-acting nature of ER/LA opioid analgesics means that ER/LA patients who suffer negative consequences from their use (e.g., the depressed breathing rate associated with an overdose) are in danger for a longer period of time than IR patients because they will continue to have circulating levels of opioid for a much longer time,

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

[40] See section 505(o)(4)(D) of the FD&C Act.

thereby increasing the likelihood of serious outcomes. Additionally, the available higher per dose strength makes ER/LA products more attractive to abusers, although the risks of misuse, abuse, addiction, overdose, and death are present for all opioids.[41]

Focusing our SLC efforts on ER/LA opioid analgesics first was not intended to preclude changes for IR opioid analgesics. Because a determination regarding the relative risks of IR and ER/LA products is not necessary to support FDA's IR opioid analgesic SLCs, this petition response need not include a detailed examination of relative risks between IR and ER/LA opioid analgesics.

IV. CONCLUSION

FDA recognizes the devastating impact that the epidemic of opioid abuse and its related risks and consequences have had on the public health. Over the past few years, the Agency has prioritized efforts to reduce the risks of opioids, and, on February 5, 2016, the Agency announced a comprehensive action plan to take concrete steps toward reducing the impact of opioid abuse on American families and communities.[42] Today, as part of that initiative, FDA has taken the next step in making these drugs safer for patients who need them by clarifying and making more prominent the risks of IR opioid analgesics.

This Petitioner has not successfully demonstrated that IR opioid analgesics "comparable or higher incidence" of risks than ER/LA opioid analgesics. However, FDA agrees that IR opioid analgesics are associated with substantial and continued abuse in the community, and that the risks of these drugs present an important public health problem that needs to be addressed. For this reason, FDA has decided to require safety labeling changes for the class of IR opioid analgesics, exercising our authority under section 505(o) of the FD&C Act. Thus, the Petition is

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[41] In support of its determination that there are disproportionate safety concerns with ER/LA opioid analgesics, FDA cited to certain data from the Drug Abuse Warning Network (DAWN) in a presentation titled, "Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network" (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf) (July 2010 Presentation), and to the inherent qualities of ER/LA opioid analgesics – namely, that ER/LA opioid analgesics are designed to release the drug over a long period of time, and that many of them contain higher doses of opioids compared to IR opioids or opioid/non-opioid combinations (see September 10, 2013 Letter to ER/LA Opioid Analgesic NDA Holders, available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf); Response to petition from Physicians for Responsible Opioid Prescribing (docket no. FDA-2012-P-0818)). Among other arguments, Petitioner disagrees with these data and with the conclusions FDA drew from them (Petition at 19-29) and argued that the data are not "objective" and lack "utility" (Petition at 26). After consulting with the Substance Abuse and Mental Health Services Administration (SAMHSA), we discovered that the classification of the IR and ER/LA opioids was incorrect in both the April 2010 and July 2010 presentations and that the nature of the misclassification differed between these two meetings. We reviewed and re-analyzed the data, and, the updated analysis in the slides still shows that, for the data analyzed, there were greater numbers of emergency department visits linked to certain ER/LA opioid analgesics than there were linked to certain IR opioid analgesics. Taken together, the updated slides and qualitative characteristics of ER/LA opioid analgesics still support the Agency's conclusion that there are disproportionate safety concerns with ER/LA opioid analgesics.

[42] See Fact Sheet – FDA Opioids Action Plan (available at http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm).

granted to the extent that the IR opioid analgesic SLCs are expected to generally "parallel" those made to the ER/LA opioid analgesics. The Petition is otherwise denied.

Sincerely,

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