

June 17, 2015

Via Electronic Submission – Regulations.gov

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Supplement to Citizen Petition, FDA-2014-P-0205

Dear Sir/Madam:

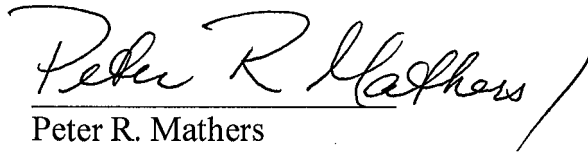
In February 2014 the undersigned submitted a Citizen Petition on behalf of Purdue Pharma L.P. requesting that the Food and Drug Administration (a) exercise its authority under Section 505(o) of the Federal Food, Drug and Cosmetic Act to seek and, if necessary, impose safety labeling changes on immediate-release opioid analgesics 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, and (b) 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. The Petition was supported by data indicating that immediate-release opioid analgesics are associated with the same potential adverse consequences as extended-release/long-acting opioid analgesics, including the risks of abuse, misuse, and overdose, with comparable if not higher incidence. The risks and corresponding public health ramifications associated with immediate-release opioid analgesics therefore should be addressed in manner consistent with the Agency's actions on extended-release and long-acting opioid analgesics, with similar label changes mandated.

On June 4, 2015, Members of Congress wrote to the Agency requesting that it exercise its authority under Section 505(o)(4) of the Federal Food, Drug and Cosmetic Act to require manufacturers of immediate-release opioid analgesics to adopt labeling that more effectively communicates the risks of abuse, neonatal abstinence syndrome, addiction, overdose, and death including the same black box warning as currently appears

on extended-release and long-acting opioid analgesics.¹ The basis for the request was (a) the lack of evidence that extended-release and long-acting opioid analgesics present greater risks of overdose, addiction, abuse, misuse, death, and neonatal abstinence syndrome, compared to immediate-release opioid analgesics, and (b) the widespread use of immediate-release opioid analgesic products, compared to extended-release and long-acting opioid analgesics. The letter requests a written response from the Agency by June 29, 2015 addressing “whether FDA plans to require the labeling change to the IR opioid formulations as we request, why or why not, and an approximate timeline for any such planned labeling change requirement”.

The Representatives’ letter, the data cited in support of it, and the anticipated Agency response to the letter are all relevant to Purdue’s pending Citizen Petition. Accordingly, Purdue submits this supplement to incorporate the Representatives’ letter into Docket FDA-2014-P-0205.

Respectfully submitted,



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¹ See Letter to Dr. Stephen Ostroff, Commissioner, U.S. Food and Drug Administration (June 4, 2015), copy attached, and available at: http://democrats.energycommerce.house.gov/sites/default/files/documents/Commissioner.Ostroff.FDA_Labeling.Letter.2015.6.5.pdf. The June 5, 2015 Press Release announcing the letter is available at: <http://democrats.energycommerce.house.gov/index.php?q=news/committee-democrats-seek-stronger-labeling-of-opioids>.

ONE HUNDRED FOURTEENTH CONGRESS
Congress of the United States
House of Representatives
COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515-6115
Majority (202) 225-2927
Minority (202) 225-3641

June 4, 2015

Dr. Stephen Ostroff
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Commissioner Ostroff:

We write to you to request that the Food and Drug Administration (FDA) invoke its authority under section 505(o)(4) of the Food, Drug, and Cosmetic Act (the FD&C Act) to require manufacturers of Immediate Release (IR) opioid analgesics to make labeling changes to more effectively communicate the serious risks of abuse, neonatal abstinence syndrome (NAS), addiction, overdose, and death associated with the use of opioid analgesics.

Given the national public health crisis of prescription drug overdoses, an issue that has been a subject of extensive examination by the House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, we believe this common sense approach would equip patients and prescribers with information necessary to make informed decisions regarding the risks of opioid analgesics.

The Centers for Disease Control and Prevention (CDC) has declared prescription drug abuse in the United States an epidemic and has found drug overdose to be the leading cause of injury death in the United States.¹ Between 2000 and 2010, there was a fourfold increase in the use of prescribed opioids for the treatment of pain.² This increase in opioid prescriptions has been mirrored by a fourfold increase in opioid-related overdose deaths: between 1999 and 2010,

¹ Office of National Drug Control Policy, *Prescription Drug Abuse* (online at www.whitehouse.gov/ondcp/prescription-drug-abuse) (accessed Mar. 17, 2015).

² Substance Abuse and Mental Health Services Administration, *SAMHSA Opioid Overdose Prevention Toolkit* (2014).

the death rate from prescription opioids more than quadrupled.³ In addition to the tragic losses of life and the impact on families and communities, the opioid abuse epidemic has had significant costs to our healthcare system. In 2010, drug overdoses from prescription opioids were involved in an estimated 80,095 hospital visits costing \$1.3 billion.⁴

The incidence of neonatal abstinence syndrome (NAS) has also skyrocketed. NAS is associated with preterm births, low birthweight, and complications such as respiratory distress and seizures.⁵ According to a recent study in the *New England Journal of Medicine*, from 2004 through 2013, the incidence of NAS quadrupled.⁶ In 2012, aggregate hospital charges for NAS were \$1.5 billion, with 81% attributed to state Medicaid programs.⁷

In 2013, in response to a citizen petition submitted by Physicians for Responsible Opioid Prescribing (PROP), the FDA adopted labeling changes to more effectively communicate to prescribers and patients the serious risks associated with opioid analgesics.⁸ The FDA required manufacturers to adopt the most restrictive language that can be found in drug labeling, a “black box” warning about their potential for abuse, the risk of fatal overdose, and a warning that maternal use of these products during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening.⁹ For example, the label for the recently approved ZOHYDRO ER extended-release capsules contains the following black box warning, in bold print:

“WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL; and CYTOCHROME P450 3A4 INTERACTION.”

³ Nora D. Volkow et. al., *Medication-Assisted Therapies – Tackling the Opioid Overdose Epidemic*, *New England Journal of Medicine* (May 29, 2014).

⁴ Michael A. Yokell et. al., *Presentation of Prescription and Nonprescription Opioid Overdoses to US Emergency Departments*, *JAMA Internal Medicine* (Oct. 27, 2014).

⁵ Stephen W. Patrick, *Neonatal Abstinence Syndrome and Associated Health Care Expenditures United States, 2000-2009*, *JAMA Internal Medicine* (May 9, 2012).

⁶ Veeral N. Tolia et. al., *Increasing Incidence of Neonatal Abstinence Syndrome in U.S. Neonatal ICUs*, *The New England Journal of Medicine* (Apr. 26, 2015) (online at www.nejm.org/doi/full/10.1056/NEJMs1500439?query=featured_home).

⁷ S.W. Patrick et al., *Increasing Incidence and Geographic Distribution of Neonatal Abstinence Syndrome: United States 2009 to 2012*, *Journal of Perinatology* (Apr. 30, 2015).

⁸ Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, to Dr. Andrew Kolodny, President, Physicians for Responsible Opioid Prescribing, Re: Docket No. FDA-2012-P-0818 (Sept. 10 2013).

⁹ *Id.*

This lead sentence is followed by additional detail regarding these risks, and recommendations for prescribers, including a recommendation that prescribers assess each patient's risk for addiction, abuse, and misuse before prescribing and monitoring patients regularly for development of these behaviors and conditions.¹⁰

However, FDA chose to apply this black box warning only to Extended Release and Long-Acting (ER/LA) opioid analgesics. The FDA letter responding to the PROP petition noted that ER/LA opioid analgesics have disproportionate safety concerns compared to IR opioids and opioid/non-opioid combination products.¹¹ The FDA cited the fact that ER/LA opioids may contain higher doses of opioids compared to IR products, and are often used in a chronic pain setting, as justification for drawing this distinction.¹²

However, as the agency also acknowledged, much of the literature FDA reviewed that provided the basis for the labeling change assessed opioid use from all opioid sources, and did not separate data according to opioid formulation.¹³ Indeed, the body of evidence regarding the association between opioid prescribing and addiction, overdoses, death, and neonatal abstinence syndrome do not favorably distinguish the IR formulations from the ER/LA formulations in terms of health outcomes.¹⁴ A recent systematic review by the Agency for Health Research and Quality (AHRQ) did not identify a single study that found statistically significant differences between short versus long-acting opioids on the risks of overdose, addiction, abuse, or misuse in patients with chronic pain.¹⁵

¹⁰ *Highlights of Prescribing Information, ZOHYDRO ER (hydrocodone bitartrate) extended-release capsules, for oral use, CII* (available at www.accessdata.fda.gov/drugsatfda_docs/label/2015/202880Orig1s003lbl.pdf) (accessed May 12, 2015).

¹¹ Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, Food and Drug Administration, to Dr. Andrew Kolodny, President, Physicians for Responsible Opioid Prescribing, Re: Docket No. FDA-2012-P-0818 (Sept. 2013).

¹² *Id.*

¹³ *Id.*

¹⁴ See, e.g., Stephen W. Patrick et al., *Prescription Opioid Epidemic and Infant Outcomes*, Pediatrics (May 2015); David N. Juurlink and Irfan a. Dhalla, *Dependence and Addiction During Chronic Opioid Therapy*, American College of Medical Toxicology 2012 (Oct. 2012); Joseph A. Boscarino et al., *Prevalence of Prescription Opioid-Use Disorder Among Chronic Pain Patients: Comparison of the DSM-5 vs. DSM-4 Diagnostic Criteria*, Journal of Addiction Diseases (July 2011); Amy S. B. Bohnert et al., *Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths*, JAMA (Apr. 6, 2011); K.M. Dunn et al., *Opioid Prescriptions for Chronic Pain and Overdose: A Cohort Study* (Jan. 2010).

¹⁵ Agency for Healthcare Research and Quality, *Evidence Report/Technology Assessment: The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain* (Sept.

Additionally, IR opioid analgesics are widely prescribed and used in the United States. According to one estimate, IR opioids represent 91% of all outpatient opioids prescribed in 2009, with ER opioids comprising 9% of prescriptions.¹⁶ For example, hydrocodone acetaminophen was the most widely prescribed drug to Medicare beneficiaries in 2013.¹⁷ In 2011, 131 million prescriptions for combination hydrocodone-containing analgesics (products containing hydrocodone as well as non-opiate drugs such as ibuprofen and acetaminophen) were dispensed in the United States, representing over 47 million patients.¹⁸

The widespread use and resulting large-scale public health impact of IR hydrocodone combination products was a factor that affected the Department of Health and Human Services' (HHS) recommendation that these products be rescheduled from Schedule III to Schedule II under the Controlled Substances Act. The Department recommended this rescheduling of hydrocodone products due to their "high potential for abuse" and the fact that their abuse "may lead to severe psychological or physical dependence." While acknowledging that hydrocodone combination products have a lower risk per exposure than products containing oxycodone, HHS observed that the huge volume of hydrocodone prescriptions in the U.S. results in a serious public health impact:

[H]ydrocodone is unlike any other opioid regarding the unprecedented number of hydrocodone prescriptions in the U.S. each year. It is this characteristic of the use of hydrocodone combination products that drives the potential for abuse of these products and sets hydrocodone apart from any other opioids in terms of risks for abuse.¹⁹

Additionally, a recent study of the Tennessee Medicaid program in *Pediatrics* found that 28% of women in the program were prescribed opioid pain relievers during pregnancy. Of the infants that were born with NAS, 65% had mothers that had received legal prescriptions for opioid pain relievers. Nearly all of the women who were legally prescribed opioids (96%) were

2014) (online at www.effectivehealthcare.ahrq.gov/ehc/products/557/1971/chronic-pain-opioid-treatment-report-140929.pdf).

¹⁶ Food and Drug Administration, *Outpatient Prescription Opioid Utilization in the U.S., Years 2000-2009* (July 22, 2010) (online at www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf).

¹⁷ *Generic Vicodin Was a Top Medicare Drug in 2013, Data Shows*, Wall Street Journal (May 4, 2015).

¹⁸ Letter from Howard K. Koh, Assistant Secretary for Health, Department of Health and Human Services to Michele M. Leonhart, Administrator, Drug Enforcement Administration, U.S. Department of Justice Re: Basis for the Recommendation to Place Hydrocodone Combination Products in Schedule II of the Controlled Substances Act (Dec. 16, 2013).

¹⁹ *Id.*

Commissioner Ostroff

June 4, 2015

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prescribed IR medications—only 0.6% were prescribed long-acting preparations.²⁰ It is critical that pregnant women and their physicians have access to clear, concise information about the risks of NAS when considering whether to prescribe opioid therapies during pregnancy, and we are concerned that the current labeling for IR opioids does not meet this threshold.

Given the established risk of addiction, abuse and overdose from all opioid analgesics, as well as the emerging public health threat of NAS, we believe that the FDA should ensure that all IR opioid formulations bear the same black box warning as the ER/LA formulations. We believe that this information is crucial to patients and prescribers, and we ask that you work expeditiously to address this issue. Please provide a response in writing by June 29, 2015, to this letter, including whether FDA plans to require the labeling change to the IR opioid formulations as we request, why or why not, and an approximate timeline for any such planned labeling change requirement.

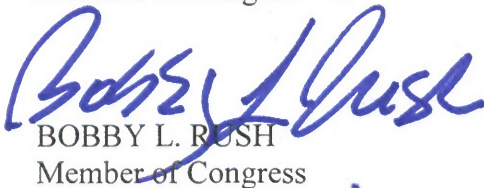
Additionally, FDA's response to the PROP petition describes a mandatory process for manufacturers of ER/LA opioids to conduct post-marketing reviews to assess the safety of long term use of opioids. The response indicates that sponsors are required to submit final study protocols to FDA by August 2014. Please provide copies of these final protocols, any finalized reports, and an update on the status of these studies, which are scheduled to be completed as early as August 2015. Please provide the requested information by no later than June 29, 2015.

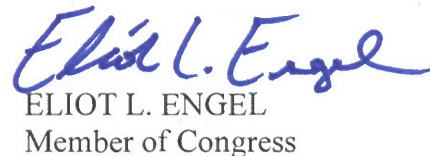
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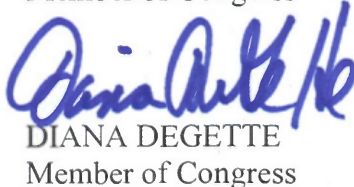
Sincerely,


FRANK PALLONE, JR.
Member of Congress


GENE GREEN
Member of Congress


BOBBY L. RUSH
Member of Congress


ELIOT L. ENGEL
Member of Congress


DIANA DEGETTE
Member of Congress


LOIS CAPPS
Member of Congress

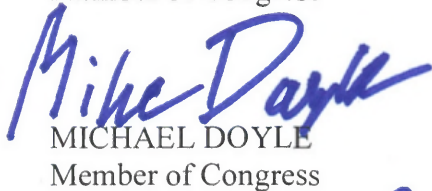
²⁰ Stephen W. Patrick et. al., *Prescription Opioid Epidemic and Infant Outcomes*, Pediatrics (May 2015).



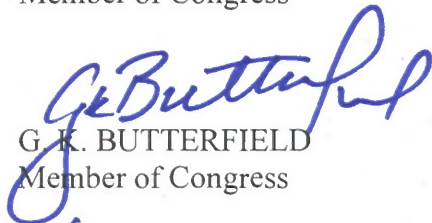
JAN SCHAKOWSKY
Member of Congress



DORIS O. MATSUI
Member of Congress



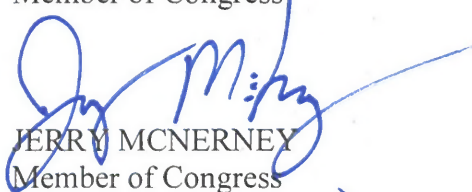
MICHAEL DOYLE
Member of Congress



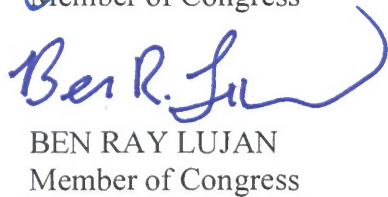
G. K. BUTTERFIELD
Member of Congress



KATHY CASTOR
Member of Congress



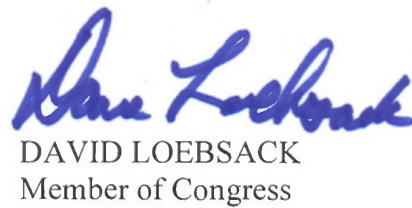
JERRY MCNERNEY
Member of Congress



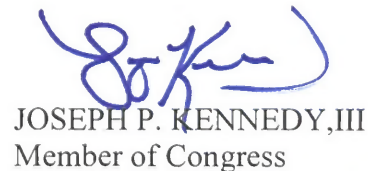
BEN RAY LUJAN
Member of Congress



JOHN YARMUTH
Member of Congress



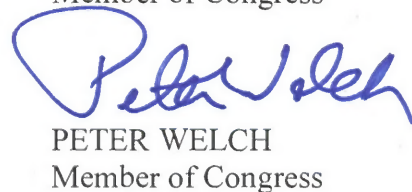
DAVID LOEBSACK
Member of Congress



JOSEPH P. KENNEDY, III
Member of Congress



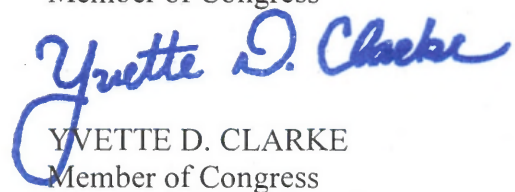
JOHN SARBANES
Member of Congress



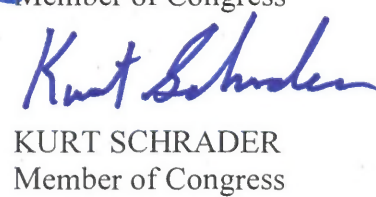
PETER WELCH
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PAUL TONKO
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YVETTE D. CLARKE
Member of Congress



KURT SCHRADER
Member of Congress



TONY CARDENAS
Member of Congress