Purdue Pharma L.P.

One Stamford Forum
Stamford, CT 06901-3431
www.purduepharma.com

January 30, 2013

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

Re: Docket ID # FDA-2012-P-0818

Purdue Pharma L.P. is submitting these comments in response to the Citizen Petition filed by Physicians for Responsible Opioid Prescribing. The Petition seeks to narrow the indication for all opioid analgesics when prescribed for non-cancer pain in three ways: (i) limit to severe pain intensity only, (ii) add a maximum duration of 90 days for continuous (daily) therapy, and (iii) add a maximum daily dose equivalent to 100 mg of morphine. While we support measures that address problems associated with the use, misuse, abuse, and diversion of opioid medications (see: www.RxSafetyMatters.com), we do not support the Petition since the label restrictions it proposes threaten access for patients with legitimate medical need and the Petition itself lacks a sound scientific foundation.

We note at the outset of these comments the supplemental submission of December 10, 2012 by which Petitioners sought to reassure patients with chronic non-cancer pain that Petitioners do not intend the changes requested in their Petition to interfere with opioid prescribing. We also note the supplemental submission of January 9, 2013 by which Petitioners state: "Our petition was filed because we believe that . . . opioid manufacturers . . . should be prohibited from misinforming clinicians and patients about the risks and benefits of opioid analgesics."

Quite apart from the lack of scientific, medical and factual validity of their assertions, Petitioners' clarification of their intent directly contradicts the relief which they seek. While purporting to preserve access of patients with chronic non-cancer pain to the safe and effective opioid treatments they and their physicians agree they need, Petitioners seek arbitrarily to remove many such safe and effective uses of opioids from the labeling of those products. In addition, rather than seeking better information for clinicians and patients about the risks and benefits of opioid analgesics, Petitioners seek to remove such information from opioid labeling and thereby severely limit the ability of manufacturers to disseminate truthful and non-misleading information about such products.

Manufacturers of opioid drug products have submitted data that meet and exceed the long-standing FDA requirements for demonstrating the safety and efficacy of opioid analgesics in the treatment of moderate, as well as severe, pain for long-term use. In addition, data have been submitted to the FDA or published in peer-review literature regarding individuals who received dosages, when appropriate, in excess of 100 mg morphine equivalents per day. There is no substantial scientific evidence of safety or efficacy problems specific to any such uses, or of an unfavorable benefit-risk balance, which would warrant their categorical exclusion from opioid labeling. Even where it may be appropriate for physicians and patients to exercise additional care or caution in treating particular types of pain, or specific patients, such uses should remain in opioid product labeling and should be appropriately addressed in treatment guidelines, REMS

educational materials, and other promotional and educational materials. Petitioners' suggested approach is not only unwarranted, but is counterproductive, in that it would limit the dissemination of information that currently exists or that may be developed in the future. Denying practitioners such information could compromise the provision of optimal care for patients who would benefit from opioid treatment.

In light of the above concerns, we set forth below a number of critical issues that should be considered in evaluating the Petition.

1. The proposed label changes are not supported by substantial clinical evidence. We oppose the requested changes as an unwarranted departure from well-established principles of regulatory science that do not serve the interest of patients or healthcare professionals. The Citizen Petition contains weak evidence and attempts to support it with flawed data analyses.

2. Undue reliance by FDA on the types of observational, retrospective, and survey data cited by Petitioners would depart from the quality and rigor of evidence currently required for changes in the Full Prescribing Information (FPI) for drug products and would set a precedent which could have far reaching implications for other medication classes.

3. The indications for most opioid analgesic drug products do not contain limitations of use for specific disease states or causes of pain, in part because of the various patient populations studied in the clinical trials required by FDA for approval. Moreover, with regard to opioid analgesics, there is no clinical or regulatory basis for an artificial distinction between cancer- and non-cancer pain, as the anatomical distribution of opioid receptors and the pharmacology of opioid analgesics do not change based on whether the pain is generated from a process related or unrelated to a cancer or its treatment.[1,2] Petitioners may be relying upon unsupported, and unstated, assumptions that patients with pain related to cancer or its treatment are either near the end of life or less susceptible to adverse events from opioid use. However, the distinction is not scientifically valid and its utility (as well as its fairness) has been questioned by experts in pain care and bioethics, particularly in light of the increasing population of cancer survivors.[3,4] Moreover, from patient, prescriber, pharmacy, and payer perspectives, attempting to make and enforce such a distinction would be fraught with problems and would be neither practical nor feasible from a health-systems standpoint. It would introduce needless discrimination, confusion, burden, and inefficiencies to the healthcare system and would inhibit access to proper and timely care for persons suffering persistent pain.

4. Prescriptions for patients who require opioid analgesic therapy outside or beyond the proposed restrictions would be considered "off label," which could affect prescribers' professional liability and, thus, their willingness or ability to provide such care. The proposed label changes would also harm patients by creating new problems with insurance coverage of opioid medicines.

5. The basis for Petitioners' recommendation to remove "moderate" pain from opioid analgesic drug products' indications in patients with non-cancer pain is unfounded, and no rationale is cited in the Petition. Opioid drug products are typically not approved for treatment of "mild" pain. However, on standard pain scales, the category of "moderate" should not be confused with "mild" or "nuisance-level" pain. Under those pain scales, which are used in clinical trials and in prescribing decisions, pain of "moderate" intensity is truly significant[5] and, especially if persistent, significantly interferes with enjoyment of life, work, mood, general activity, and sleep.[6] There is substantial clinical evidence establishing the safety and efficacy of opioid analgesics in patients with moderate to severe pain[7-21] and no basis on which to deny opioid treatment to patients with moderate non-cancer pain (or cancer pain) for whom such treatment may be their best therapeutic choice. Moreover, the indication for extended-release/long-acting ("ER/LA") opioid analgesics is limited to patients whose pain meets a three-part indication, namely: 1) moderate to severe pain, 2) when a continuous, around-the-clock opioid analgesic is needed 3) for an extended period of time.[22, 23]

6. The recommendation to impose a maximum daily dose equivalent to 100 mg of morphine for non-cancer pain is arbitrary and unwarranted. The epidemiology studies cited in the Petition have several limitations, including basing the study conclusions on the doses of opioids prescribed as distinct from the doses actually taken. Additionally, these studies employed an arbitrary upper dosing threshold of $\geq$ 100 mg, which does not allow determination of a meaningful dose-response or dose-risk relationship with respect to higher opioid doses. The utility of the studies cited by Petitioners is further hampered by the pooling of opioid drug products, which introduces potential biases due to differences in indications, formulations, and opioid drug substances among patients receiving higher versus lower doses (confounding by indication) because those receiving lower daily doses usually differ from patients prescribed higher doses in terms of pain (severity, pattern, impact, and duration), opioid drug substances prescribed, and formulation prescribed (immediate-release versus ER/LA). At any prescribed dose, the risk of overdose is controlled not by arbitrary dosage limitations, but by good prescribing practice and patient monitoring, including prescribing higher doses only to opioid-tolerant patients who require such doses to control their pain, and being cognizant of concomitant medications the patient is taking. Thus, adopting an arbitrary limitation on total daily opioid dose merely assures the ineffective treatment of many patients or, contrary to logic and appropriate regulatory policy, assumes that the limitation will be ignored by prescribers whenever necessary -- to properly treat their patients' pain.

7. The recommendation to impose a maximum duration of 90 days of opioid treatment for non-cancer pain is also arbitrary and not based on substantial clinical evidence. Petitioners state that the "Long-term safety and effectiveness of managing CNCP (chronic non-cancer pain) with opioids has not been established." However, they ignore the fact that data on long-term opioid use do exist and those data support the use of opioids beyond 90 days.[14, 24-39] Moreover, Petitioners fail to present any data suggesting that there is any alternative treatment for chronic, moderate to severe pain which is safer or more effective for all, or any defined category of, patients – data which would be necessary before FDA could reasonably consider restricting the use of opioids in those

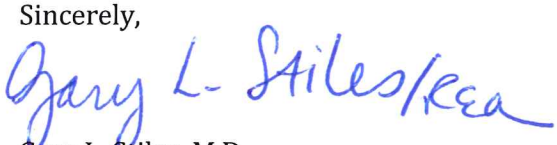
patients. In the absence of such alternatives, imposing a limitation would deprive patients who benefit from opioids of such therapy. Petitioners do not comment on the fate of patients whose pain is successfully managed with opioid analgesic therapy for 90 days who, for insurance coverage reasons or practitioner concern over malpractice or regulatory risks stemming from off-label opioid prescribing, could be required to discontinue such therapy if Petitioners' proposals were adopted.

8. While approved extended-release opioid analgesics have been evaluated in numerous clinical studies to show safety and efficacy, and have been approved by FDA for use in treating chronic pain, we would welcome and support the development of additional clinical data, in collaboration with FDA, other government agencies, academia, pain management clinicians, and pharmaceutical manufacturers, to further address the benefits and risks of opioid therapy. We believe this research, along with education, would further assist healthcare professionals with patient assessment, selection, treatment planning, ongoing monitoring, and control of treatment risks.

9. The recently-approved ER/LA Opioid Analgesics REMS has been designed, at FDA's direction, to provide independent, comprehensive education to prescribers of opioid drug products. This REMS education initiative, and related clinical treatment guidelines, provides appropriate means for conveying consensus-based information about appropriate opioid prescribing practices within the scope of the FDA-approved labeling. As the first industry-funded REMS-compliant continuing education programs will become available shortly, there is no basis yet to assess their effectiveness. Moreover, the White House Office of National Drug Control Policy has stated its desire to see opioid-related education become a pre-requisite for practitioners to lawfully prescribe these medicines, which would undoubtedly extend the reach of these enhanced educational efforts. These and other modifications to the REMS education initiatives, and ongoing evolution of expert consensus-based treatment guidelines, provide an appropriate and far better alternative to conveying information about appropriate prescribing practices than would adopting unwarranted and unsupported, arbitrary label restrictions -- that would exclude large categories of patients with pain from the scope of approved opioid treatment. This is particularly so since such exclusion would limit – not expand – the dissemination of information about the appropriate use of opioids in treating such patients or, contrary to the express intention of Petitioners, limit the availability of opioid treatments to some of the very patients who need them.

For the forgoing reasons, FDA should refrain from changing any opioid FPI unless substantial clinical data is presented that provides clear justification for doing so and, in light of the existing data, FDA should refuse to make the changes requested by Petitioners.

Sincerely,



Gary L. Stiles, M.D.
Senior Vice President, Research and Development
Purdue Pharma L.P.

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Pivotal Trials from FPIs

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Duration: 12 weeks (double-blind treatment phase)

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Duration: 12 weeks – (double-blind maintenance)

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Duration: 12 weeks (double-blind maintenance)

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severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. *Clin Drug Investig*. 2010;30(8):489-505.
Duration: 12 weeks (double-blind maintenance)

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Duration: 8 weeks (4 weeks per treatment)

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Duration: 7 weeks (1-week run-in, 6-week treatment phase)

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Duration: 4 weeks

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Duration: 30 weeks (4-week double-blind, 26-week open-label extension)

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Duration: 12 weeks (double-blind treatment period)

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Duration: 12 weeks (double-blind treatment period)

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Duration: 12 weeks (maintenance phase)

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Duration: 24 weeks

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Duration: 90 days

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Duration: 17 weeks (5-week pre-randomization, 12-week double-blind treatment)

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Duration: 12 weeks (double-blind treatment period)

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Duration: up to 3 years

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Duration: 2 weeks + 18 month extension

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Duration: 6 months (1-month titration, 5-month maintenance)

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Duration: 1 year

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Duration: 52 weeks (1-week titration, 51-week maintenance)

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Duration: 13 months

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Duration: 2 years

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Duration: 6 months

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Duration: 9 months

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Duration: up to 12 months

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Duration: up to 48 months (data analyses – baseline up to 12 months)

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Duration: 32 weeks (mean duration of opioid treatment)

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Duration: 6 months

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Duration: 162 days (mean duration BTDS exposure); up to 12 months

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Duration: 22 months

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Duration: 52 weeks