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**Via Hand Delivery**

Division of Dockets Management  
 Food and Drug Administration  
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 5630 Fishers Lane, Room 1061 (HFA-305)  
 Rockville, MD 20852

**Re: Comments on Docket No. FDA-2008-P-0618**

Dear Sir or Madam:

Purdue Pharma L.P. ("Purdue") submits these comments in opposition to the citizen petition filed on November 26, 2008, by Philip W. Thomas on behalf of Patricia Gwen Kiser (the "Petitioner").<sup>1</sup> The Petition requests the Food and Drug Administration ("FDA") to revoke approval of the current package insert for the prescription drug OxyContin® (oxycodone HCl controlled-release) tablets; declare the OxyContin package insert misleading; and require Purdue to revise the package insert to (i) remove the "log scale graph" set forth in the pharmacokinetics section of the labeling,<sup>2</sup> (ii) disclose dysphoria as an adverse experience, and (iii) more prominently disclose the adverse risks of euphoria and dysphoria in a black box warning.<sup>3</sup> According to the Petition, these revisions are necessary to ensure that the approved labeling for OxyContin provides accurate information about the risks of abuse, physical dependence and addiction associated with the drug.

Because Petitioner has failed to provide any evidence that OxyContin's FDA-approved labeling is false or misleading with respect to the risks of abuse, physical dependence or addiction, the Petition should be denied. Contrary to Petitioner's allegations, the approved labeling for OxyContin clearly, accurately and repeatedly warns prescribers in a boxed warning

<sup>1</sup> Docket No. FDA-2008-P-0618 (Nov. 26, 2008) (hereinafter the "Petition").

<sup>2</sup> Although Petitioner refers to the graph as a "log scale" graph, it is, in actuality, a "semi-log scale" graph because only the y-axis is scaled logarithmically. For accuracy's sake, we will refer to the graph as a "semi-log scale graph."

<sup>3</sup> The Petition also requests that FDA take these actions with respect to OxyContin's approved "drug label." Because OxyContin's approved drug "label" does not contain the semi-log scale graph, a list of adverse reactions, or a boxed warning, Purdue assumes that Petitioner meant to refer to OxyContin's "labeling" rather than its "drug label." See 21 U.S.C. §§321(k), (m) (distinguishing between the terms "label" and "labeling"). To the extent Petitioner intended to refer to OxyContin's drug "label," the Petition should be denied (a) as moot, because the label does not include a semi-log scale graph or adverse reaction information; (b) as inconsistent with FDA's regulations governing the content of the drug label, which do not require black box warnings or adverse event information (see 21 C.F.R. §§201.56, 201.57, 201.100); and (c) as unsupported and unjustified, for the reasons discussed in the body of this response with respect to the package insert.

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and elsewhere that “OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.”<sup>4</sup> The semi-log scale graph makes no claims, either express or implied, regarding the risks of abuse, dependence or addiction of OxyContin and instead serves simply as a means of illustrating the dose proportionality of the various strengths of OxyContin, consistent with current FDA guidance. Likewise, the Adverse Reactions section of the labeling is based upon the clinical trials supporting approval of OxyContin and relevant post-market experience, and Petitioner has provided no evidence that “dysphoria” should be listed as an adverse event. Finally, Petitioner’s request must fail because it does not satisfy the requirements of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (“FFDCA”), which governs the issuance of safety labeling orders of the type requested by Petitioner.

Although Purdue respectfully opposes the Petition as deficient on both factual and legal grounds, Purdue stresses that it is fully committed to ensuring that OxyContin’s FDA-approved labeling is complete and accurate and contains all necessary directions and warnings to ensure the safe and effective use of OxyContin. Purdue’s detailed comments opposing the Petition are set forth below.

### **I. Background Information Regarding OxyContin**

Purdue is the holder of the new drug application (“NDA”) for OxyContin. NDA 20-553 for OxyContin was approved on December 12, 1995. At the time of the initial approval, three strengths were approved: 10, 20 and 40 mg. Since the time of the initial approval, five additional strengths have been approved: 15, 30, 60, 80 and 160 mg strengths. OxyContin is an opioid analgesic that is indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The labeling provides that “[t]he controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours.”<sup>5</sup>

### **II. The Approved Labeling for OxyContin Clearly and Accurately Warns Physicians About the Risks of Abuse, Dependence and Addiction.**

Throughout the Petition, Petitioner attempts to demonstrate that the FDA-approved labeling for OxyContin is misleading with respect to the risks of abuse, dependence and addiction associated with the drug. To do this, Petitioner focuses on two discrete sections of the OxyContin labeling: (a) the semi-log scale graph contained in the Pharmacokinetics section of the labeling; and (b) the absence of the term “dysphoria” in the Adverse Reactions section of the labeling. While these sections are a part of the important labeling information – and are

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<sup>4</sup> Approved Package Insert for OxyContin® (oxycodone HCl controlled-release) tablets (Nov. 5, 2007) (“Package Insert”), at 1.

<sup>5</sup> *Id.* at 21.

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discussed in more detail below – they are not meant to be and should not be viewed in isolation. Rather, their significance (or lack thereof) with respect to the risks of abuse, dependence and addiction can be accurately assessed only when they are placed in proper context in light of the rest of the package insert. When viewed this way, it becomes evident that, contrary to Petitioner’s assertions, both express and implied, the approved labeling for OxyContin clearly, accurately and repeatedly warns prescribers that OxyContin entails significant risks of abuse, dependence and addiction.

The first and most conspicuous warning regarding the abuse liability of OxyContin is the “CII” symbol that appears in bold lettering adjacent to the drug’s name and dosage forms, which identifies the product as a Schedule II controlled substance.<sup>6</sup> Because OxyContin is a Schedule II controlled substance, the only physicians allowed to prescribe it are those who have applied for and received a license from the Drug Enforcement Administration.<sup>7</sup> Such physicians understand that the Schedule II designation is reserved for drugs that have a “high potential for abuse” and that carry risks of “severe psychological or physical dependence.”<sup>8</sup> Consequently, the “CII” symbol in the OxyContin labeling serves as a strong warning to physicians and other prescribers of the drug’s Schedule II controlled substance status.<sup>9</sup>

Another prominent warning regarding the abuse liability of OxyContin is contained in the drug’s boxed warning on the first page of the FDA-approved package insert. The labeling states, in bold lettering, that:

**OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.**<sup>10</sup>

The boxed warning further states in standard lettering that “[o]xycodone can be abused in a manner similar to other opioid agonists, legal or illicit[.]” and that this should be considered when prescribing or dispensing OxyContin in situations where there is “an increased risk of misuse, abuse, or diversion.”<sup>11</sup>

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<sup>6</sup> *Id.* at 1. See 21 U.S.C. §812(a) (requiring that controlled substances are labeled with an identifying symbol in accordance with applicable regulations).

<sup>7</sup> See 21 C.F.R. §1306.03(a)(2).

<sup>8</sup> 21 U.S.C. §812(b)(2).

<sup>9</sup> Schedule II controlled substances are subject to a high degree of regulation, including strict control over the prescribing and dispensing of such substances by physicians and pharmacists. See, e.g., 21 C.F.R. §§1306.11-1306.15.

<sup>10</sup> Package Insert at 1.

<sup>11</sup> *Id.*

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As FDA acknowledges, “[a] boxed warning is the most serious warning placed in the labeling of a prescription medication.”<sup>12</sup> According to FDA regulations, “[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.”<sup>13</sup> A boxed warning must be presented in approved labeling before any other drug information, including the indication.<sup>14</sup> Indeed, the two warnings quoted above are the first two sentences presented in OxyContin’s FDA-approved labeling, clearly informing physicians that OxyContin carries significant risks regarding abuse, dependence and addiction.

OxyContin’s FDA-approved labeling contains numerous additional warnings that further emphasize the risk of abuse associated with the drug. Warnings emphasizing the abuse potential include the following:

- The Warnings section contains an in-depth discussion of the risks of “Misuse, Abuse and Diversion of Opioids,” disclosing that oxycodone, the active ingredient in OxyContin, “is an opioid agonist of the morphine-type” that is often sought by “drug abusers and people with addiction disorders . . .”<sup>15</sup>
- The Warnings section further states that “[o]xycodone can be abused in a manner similar to other opioid agonists, legal or illicit.”<sup>16</sup>
- In the Warnings section, under the prominent heading “Drug Abuse and Addiction,” the labeling provides in bold lettering: “**OxyContin contains oxycodone, which is a full mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.**”<sup>17</sup>

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<sup>12</sup> FDA Response to Petition from Connecticut Attorney General Richard Blumenthal, Docket No. FDA-2004-P-0294, at 2 (Sept. 9, 2008) (“FDA Response to Connecticut”).

<sup>13</sup> 21 C.F.R. §201.57(c)(1).

<sup>14</sup> *Id.*

<sup>15</sup> Package Insert at 10.

<sup>16</sup> *Id.*

<sup>17</sup> *Id.*

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- The Precautions section of the labeling contains “Information for Patients/Caregivers,” which states: “Patients should be advised that OxyContin is a potential drug of abuse.”<sup>18</sup>
- The Dosage and Administration section contains the following statement in all-capital, bolded lettering, which is similar to warnings contained in the Boxed Warning and Drug Abuse and Addiction sections of the labeling: **“OXYCONTIN IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.”**<sup>19</sup>
- There are two separate warnings in the labeling regarding the risks associated with taking broken, chewed, or crushed OxyContin tablets, which is a form of abuse of the drug that disarms its timed-release mechanism. The warnings state, in all-capital, bolded lettering: **“OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.”**<sup>20</sup>
- The Patient Information Sheet contained in the labeling contains several warnings regarding the abuse potential of the drug, including a statement that “OxyContin contains a narcotic painkiller that can be a target for people who abuse prescription medicines.”<sup>21</sup> It also instructs patients to inform their doctors of any “past or present substance abuse or drug addiction”<sup>22</sup> and warns them that, “[i]f [they] have abused drugs in the past, [they] may have a higher chance of developing abuse or addiction again while using OxyContin.”<sup>23</sup>

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<sup>18</sup> *Id.* at 14.

<sup>19</sup> *Id.* at 20.

<sup>20</sup> *Id.* at 1 and 20.

<sup>21</sup> *Id.* at 28.

<sup>22</sup> *Id.* at 29.

<sup>23</sup> *Id.* at 30.

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Warnings throughout the labeling that emphasize the risks of dependence and addiction associated with OxyContin include the following:

- The Drug Abuse and Addiction section informs prescribing physicians that “[t]here is a potential for drug addiction to develop following exposure to opioids, including oxycodone.”<sup>24</sup>
- The labeling contains an in-depth discussion of addiction and physical dependence, explaining that “[p]hysicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts” and that “abuse of opioids can occur in the absence of true addiction . . . .”<sup>25</sup>
- The Precautions section of the labeling contains a general heading for “Tolerance and Physical Dependence” which states: “Physical dependence and tolerance are not unusual during chronic opioid therapy.”<sup>26</sup>
- The Overdosage section contains additional information regarding dependence, including associated withdrawal symptoms, stating: “In patients who are physically dependent on any opioid agonist, including OxyContin, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered.”<sup>27</sup>
- Finally, the Dosage and Administration section contains instructions for tapering OxyContin therapy in patients who exhibit physical dependence: “When the patient no longer requires therapy with OxyContin Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.”<sup>28</sup>

Clearly, OxyContin’s FDA-approved labeling is replete with warnings regarding the risks of abuse, dependence and addiction associated with opioid agonists like oxycodone. Petitioner’s myopic focus on the semi-log scale graph and the specific manner in which adverse reaction

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<sup>24</sup> *Id.* at 11.

<sup>25</sup> *Id.*

<sup>26</sup> *Id.* at 14.

<sup>27</sup> *Id.* at 20.

<sup>28</sup> *Id.* at 25.

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information is presented thus is misplaced. The semi-log scale graph and statements of non-serious adverse reactions are not intended to inform prescribing physicians about the abuse liability of OxyContin and are, in any event, overshadowed by the extensive information concerning the risks of abuse, dependence and addiction in the Boxed Warning, Warnings, Precautions, Overdosage and Dosage and Administration sections and Patient Information Sheet of the approved labeling. The Petition, however, ignores these repeated and conspicuous warnings.

Even if one were to view the semi-log scale graph and Adverse Reactions section in isolation, as Petitioner invites, the Petition nevertheless should be denied because it fails to provide any evidence that those portions of the labeling are false or misleading. As discussed further below, both sections accurately reflect the existing scientific information concerning dose proportionality and adverse events, respectively, and are consistent with applicable FDA regulations and guidance documents. Consequently, the Petition should be denied.

### **III. The Petition Fails To Provide Sufficient Evidence That the Semi-Log Scale Graph is Misleading With Respect to the Abuse Liability of OxyContin.**

The Petition asserts that the semi-log scale graph depicted in the “Pharmacokinetics and Metabolism” section of the OxyContin labeling is misleading because it “graphically suggests less potential for euphoria and sedation and, therefore, less potential for addiction” than immediate-release opioid products.<sup>29</sup> According to the Petition, “[p]utting the OxyContin blood plasma graph in log scale rather than mean scale flattened the curves and caused the graph to depict lower peaks and higher troughs.”<sup>30</sup> Because “peaks and valleys of blood plasma levels” have, according to the Petition, a “direct connection to euphoria and sedation,” the flatter and smoother semi-log scale graph allegedly suggests that OxyContin has lower risks of abuse, dependence and addiction than immediate-release opioid products.<sup>31</sup> As discussed further below, however, the Petition lacks factual support for its contention, and its analysis is flawed.

#### **A. The Use of a Semi-Log Scale Graph Is Appropriate for Pharmacokinetic Data Demonstrating Dose Proportionality.**

Contrary to the Petition’s allegations, the semi-log scale graph makes no claims, either express or implied, regarding the abuse liability of OxyContin and instead serves simply as a means of illustrating the dose proportionality of the various strengths of OxyContin, consistent with current FDA guidance. The graph is exactly what it purports to be: a graphic representation

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<sup>29</sup> Petition at 10.

<sup>30</sup> *Id.* at 9. The Petition refers to the alternative to the log scale graph as a “mean scale” graph. However, Purdue is not familiar with the term “mean scale” graph. The alternative to log scale is *linear* scale, which is a scale in which the divisions are uniformly spaced. These comments thus will use the term “linear scale” rather than “mean scale.”

<sup>31</sup> *Id.* at 10.

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of plasma oxycodone concentration by time. It is designed to demonstrate graphically the clinically significant fact that the various strengths of OxyContin are dose proportional, that is, that blood concentrations increase in a manner that is proportional to the strength of the dose. For an opioid drug like OxyContin that has no dose ceiling and requires individualized titration, information regarding dose proportionality is especially important for prescribing physicians.

In a recent draft guidance, FDA recommended that manufacturers use graphs and/or tables to simplify and clarify information contained in the clinical pharmacology section of a drug's labeling.<sup>32</sup> In particular, FDA advised that graphs and tables depicting pharmacokinetic attributes and exposure- or dose-response relationships can be helpful in simplifying and clarifying the labeling.<sup>33</sup> By graphically representing the dose-proportionality of OxyContin, the semi-log scale graph, located in the Clinical Pharmacology section of the drug's labeling, is consistent with this guidance.

The use of a semi-log scale graph, rather than a linear scale graph, is appropriate in this case because of the wide range of values covered by the various dosage strengths and the need to graphically depict dose proportionality between those strengths. While the use of a linear scale graph also would have been scientifically accurate, the presentation of pharmacokinetic data for OxyContin in a semi-log scale graph to graphically illustrate dose proportionality was and remains appropriate.

A logarithmic, or log, scale is a scale of measurement that distributes values based on the logarithm of a measurement instead of on the measurement itself. The spacing of graduations along a log scale may be fixed, in which case successive graduations differ by a fixed ratio. Alternatively, graduations along a log scale may be spaced in proportion to the logarithm of the values represented, in which case successive graduations differ by a fixed amount. If only the abscissa or ordinate (x- or y-axis) is scaled logarithmically, the plot is referred to as a semi logarithmic, or semi-log, plot.

As even the Petition acknowledges, a log scale can be a useful form of presentation of data when the data covers a large range of values.<sup>34</sup> The logarithm reduces this range to a more manageable range and provides a means of viewing the data that allows the values to be discerned from the graph. Pharmacokinetic data is commonly presented in log or semi-log scale. For example, the package insert for Fentora®, another opioid drug product, uses a semi-log scale graph to compare blood concentration levels following administration of various doses of the

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<sup>32</sup> *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Draft) (Feb. 2009), at 11.

<sup>33</sup> *Id.*

<sup>34</sup> See Petition at 8 (stating that “a logarithmic scale allows the presentation of data that covers a large range of values”).

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drug.<sup>35</sup> See Fentora package insert excerpt (attached at Tab A). In the semi-log scale graph that appears on page 8 of the package insert, blood concentration (y-axis) is plotted against time (x-axis) for an 8-fold dose range, and the graph has evenly spaced major intervals that differ by a fixed factor of 10x. Similarly, Goodman & Gilman's, *The Pharmacological Basis of Therapeutics*, uses semi-log scale graphs to depict plasma concentration versus time following administration of a drug, with evenly spaced intervals that differ by a fixed factor of 2x.<sup>36</sup> See excerpt from Goodman & Gilman's, *The Pharmacological Basis of Therapeutics* (attached at Tab B) (presenting semi-log scale graphs in a non-commercial, non-labeling context). As these examples illustrate, the semi-log scale graph is appropriate for comparing pharmacokinetic values for multiple dosage strengths of a drug product.

In the case of OxyContin, the range of values between the 10 mg and 160 mg strengths is large and would be difficult to depict in a linear scale graph without significant compression of data at the lower doses. Indeed, if the data were presented on a linear scale, the lower dose data (10 mg, 10 mg steady-state, and 20 mg) would appear to be flatter than in the semi-log scale graph and would fall extremely close to the baseline, making it more difficult to distinguish between the three plasma concentration curves. This phenomenon is illustrated in Figure 1 (Tab C).

A semi-log scale graph preserves the shape of a curve across different dosing ranges and thus is useful in graphically depicting dose proportionality. If a drug product such as OxyContin demonstrates dose proportionality, the plasma concentration curves nevertheless will appear disparate (rather than proportional) on a linear scale graph. This is because the lower dose curves will always appear flatter than the higher dose curves because of issues with scaling. With a semi-log scale graph, however, the shape of the plasma concentration curves is maintained across all dose ranges. This phenomenon is illustrated in Figure 2 (Tab D). While both linear and semi-log scale graphs accurately present the available data, the semi-log scale graph, by maintaining the shape of the curves across different dosage ranges, appropriately illustrates the concept of dose proportionality.

Finally, the Petitioner's contention that use of a semi-log scale graph "flattened the blood plasma curves in the graph" is simply not accurate.<sup>37</sup> While the higher strength curves may be flatter in a semi-log scale graph, the lower strength curves (10 mg, 10 mg steady-state, and 20 mg) are actually rounder. Ironically, if Purdue were to adopt a linear scale graph as requested by Petitioner, the lower dose curves would become much flatter, would tend to compress near the x-axis, and thus could be more difficult to distinguish from one another than in a semi-log scale

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<sup>35</sup> See Package Insert for Fentora® (fentanyl buccal tablet) (labeling supplement approved on Feb. 7, 2008), at 8, available at <http://www.fda.gov/cder/foi/label/2008/021947s0061bl.pdf>.

<sup>36</sup> See Goodman & Gilman's, *The Pharmacological Basis of Therapeutics* (Joel G. Hardman et al. eds., McGraw-Hill Companies, Inc. 10th ed. 2001), at 21.

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graph. Consequently, a semi-log scale graph for presenting pharmacokinetic data is, in this case, an appropriate choice.

**B. The Semi-Log Scale Graph Does Not Make Comparative Abuse Liability Claims But Rather Accurately Depicts Dose Proportionality Among OxyContin's Different Strengths.**

Despite the clear purpose of the graph to illustrate dose proportionality, and the fact that it is clearly labeled on the y-axis as being in "log scale," the Petition contends that the semi-log scale graph actually is intended to make superiority claims regarding the risks of abuse, dependence and addiction associated with OxyContin versus immediate-release opioids. This allegation, however, is belied by several features of the approved labeling. First, the semi-log scale graph does not contain any information whatsoever regarding immediate-release opioids but instead is limited to data comparing the various strengths of OxyContin.<sup>38</sup> Without data on immediate-release opioids, it simply is not possible for the semi-log scale graph to make comparative claims, either express or implied, regarding OxyContin and other opioids, as the Petition alleges.

Second, the graph is focused primarily on plasma concentration data from pharmacokinetic studies involving a *single dose* of the five depicted strengths of OxyContin. Because OxyContin is indicated for use over an extended period of time during which patients would quickly reach steady-state blood concentrations, single dose studies would have little or no relevance to the issue identified in the Petition, i.e., the magnitude of the "peaks and valleys" associated with real-world treatment. Single dose studies, however, are directly relevant to the issue of dose proportionality.

Finally, the labeling text preceding the semi-log scale graph, and the table following it, both disclose that OxyContin and immediate-release oxycodone were found in a comparative pharmacokinetic study "to be equivalent for AUC and Cmax, and similar for Cmin (trough) concentrations."<sup>39</sup> Although those additional data are not also included in the semi-log scale graph, this conspicuous disclosure in nearby text regarding the similar pharmacokinetic profiles of OxyContin and immediate-release oxycodone undercuts the Petition's unsupported assertion that the semi-log scale graph "graphically suggests less potential for euphoria and sedation and, therefore, less potential for addiction."<sup>40</sup> Rather, the FDA-approved labeling clearly discloses that the pharmacokinetic profiles of OxyContin and immediate-release oxycodone are similar in important respects.

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<sup>37</sup> Petition at 9.

<sup>38</sup> See Package Insert at 5-6.

<sup>39</sup> *Id.* at 5.

<sup>40</sup> Petition at 10.

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**C. OxyContin's Labeling Has Included a Semi-Log Scale Graph Since 1995 Without Objection From FDA.**

FDA has reviewed and approved the OxyContin labeling on several occasions since its initial approval in 1995 and has never suggested that the semi-log scale graph is false or misleading, nor that it needs to be removed or revised in any way. Indeed, the OxyContin labeling has been reviewed and approved by FDA on at least seven separate occasions.<sup>41</sup> At no point during these discussions did the Agency question or object to the use of the semi-log scale graph.

On the contrary, during the initial review of the labeling in 1995, the FDA reviewer responsible for the Pharmacokinetics section provided comments on that section of the labeling and even suggested an appropriate placement for the graph. Attached at Tab E is a copy of the reviewer's comments, which indicate that the "Graph from PI" (i.e., the semi-log scale graph) should follow the discussion of "Absorption." As shown, the reviewer made comments throughout the draft Pharmacokinetics section but did not comment on the semi-log scale graph, except to note a suggested placement for the graph.

In addition, during the final phases of FDA's review of the labeling in 1995, after an FDA "labeling day," FDA sent Purdue a version of the labeling that included the semi-log scale graph. FDA had reviewed the entire draft labeling and directed Purdue to revise the draft in numerous respects as warranted – FDA did not, however, in any way direct or suggest that the semi-log scale graph should not be included or should be revised in any way. Attached at Tab F is a copy of the revised draft labeling received by Purdue from FDA (the semi-log scale graph appears on page 3).

**IV. The OxyContin Labeling Accurately Reflects the Adverse Experience Profile of OxyContin in Accordance with FDA Requirements and the Available Scientific Information.**

The Petition requests FDA to order Purdue to add "dysphoria" as an adverse reaction on the OxyContin labeling. Consistent with FDA requirements, the Adverse Reactions section of OxyContin's FDA-approved labeling is based upon the clinical trials supporting approval of OxyContin and relevant post-marketing experience. The Petition provides no contrary evidence to support the claim that "dysphoria" should be listed as an adverse event. Accordingly, the Petition's request to add dysphoria to the Adverse Reactions section of the labeling should be denied.

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<sup>41</sup> Labeling revisions have been approved by FDA on the following dates: Dec. 12, 1995 (initial approval), June 21, 1996 (Supplement No. 001), July 25, 1997 (Supplement No. 004), July 18, 2001 (Supplement No. 022), Jan. 15, 2002 (Supplement No. 024), Nov. 20, 2003 (Supplement No. 035), and June 2, 2008 (Supplement No. 059).

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**A. FDA's Requirements Regarding the Adverse Reactions Section of Labeling.**

According to FDA regulations, the Adverse Reactions section of labeling must “describe the overall adverse reaction profile of the drug based upon the entire safety database.”<sup>42</sup> The safety database includes information from both clinical trials and spontaneous reports from postmarketing experience. Of the two types of information, “[t]he presentation of adverse reactions identified from clinical trials is the major component of the Adverse Reactions section.”<sup>43</sup> Sponsors are directed to list adverse events that occurred in clinical trials “at or above a specified rate appropriate to the safety database,” as well as some adverse events that occurred below the specified rate.<sup>44</sup>

Significantly, the regulatory definition of “adverse reaction” does not include all adverse events observed during use of a drug. Rather, it is limited to “those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.”<sup>45</sup> According to FDA, “[l]engthy lists of adverse events unlikely to have been caused by the drug are of little or no value to prescribers, and are therefore inappropriate for inclusion in labeling.”<sup>46</sup>

**B. The OxyContin Labeling Accurately Reflects the Adverse Reaction Profile of OxyContin Based Upon Clinical Trials and Postmarketing Experience.**

The current labeling for OxyContin complies with the applicable regulations and guidance documents because it lists the adverse reactions that were identified in clinical study reports for the clinical trials supporting the approval of the drug and in post-market adverse event reports. Specifically, the Adverse Reactions section of the OxyContin labeling lists (1) the most common adverse events reported in clinical trials (i.e., those with an incidence greater than 5%); (2) less common adverse events reported in clinical trials (i.e., those with an incidence between 1% and 5%); and (3) infrequent adverse events reported in clinical trials (i.e., those with an incidence less than 1%) and those reported in postmarketing experience (i.e., spontaneous reports).

“Dysphoria” is not listed as an adverse reaction in the package insert because it was not reported in the clinical study reports for the clinical trials of OxyContin at or above the relevant incidence rate. Although low-frequency events can sometimes be listed in the Adverse

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<sup>42</sup> 21 C.F.R. §201.57(c)(7).

<sup>43</sup> *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Jan. 2006), at 3 (“*Adverse Reactions Section Guidance*”).

<sup>44</sup> 21 C.F.R. §201.57(c)(7)(ii)(A); *Adverse Reactions Section Guidance*, at 2.

<sup>45</sup> 21 C.F.R. §201.57(c)(7).

<sup>46</sup> *Adverse Reactions Section Guidance*, at 5.

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Reactions section, this type of listing is usually limited to *serious* adverse events, since these may be clinically meaningful despite their rarity. FDA cautions that “[n]on-serious, low-frequency adverse events should be listed only when there is *strong* evidence that the drug caused the event,” such as a marked imbalance in the incidence rates in large controlled trials.<sup>47</sup> Because dysphoria was not listed in the clinical study reports, there was no justification for including it as an adverse reaction based upon the clinical studies supporting the approval of OxyContin.

Furthermore, as discussed in more detail below in Section IV.C., even though “dysphoria” is not itself listed as an adverse reaction in the OxyContin labeling, several more specific terms that commonly appear in definitions of “dysphoria,” or that are closely related to such terms, *were* identified in the clinical study reports and *are* included in the labeling. The more precise and descriptive terms used in the labeling more accurately depict the adverse reactions experienced by patients and may be more meaningful to physicians than simply categorizing such reactions under the general “dysphoria” label.

Likewise, there is currently insufficient information for including “dysphoria” as an adverse reaction based upon postmarketing experience. FDA states that decisions to include an adverse event from spontaneous reports are typically based upon several factors, including (a) the seriousness of the event; (b) the number of reports; and (c) the strength of the causal relationship to the drug.<sup>48</sup> In this case, dysphoria is not, in and of itself, a serious adverse event,<sup>49</sup> and Purdue has received few reports of dysphoria from postmarketing spontaneous reports.<sup>50</sup>

Finally, “[FDA] reviewer and applicant judgment remain critical in assessing how or whether to present information on an adverse reaction.”<sup>51</sup> Sponsors must balance the need to

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<sup>47</sup> *Id.* at 6 (emphasis added).

<sup>48</sup> *Id.* at 8.

<sup>49</sup> FDA regulations define a “serious adverse drug experience” as “[a]ny adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.” 21 C.F.R. §§314.80(a), 312.32(a). FDA has also advised that a “serious adverse reaction” refers to any reaction occurring at any dose that results in any of the aforementioned outcomes. *See Adverse Reactions Section Guidance*, at 13. *See also* List of MedDRA Preferred-Terms to be Considered “Serious” Based on WHO-ART Critical-Terms. Council for International Organisations of Medical Sciences. *Current challenges in pharmacovigilance: pragmatic approaches. Report of CIOMS working group V*. Geneva: CIOMS, 2001.

<sup>50</sup> While Purdue has received few reports of dysphoria (coded as “dysphoria”) from postmarketing spontaneous reports, it has received reports of other reactions that may be similar or related to dysphoria, such as nervousness, anxiety, agitation, depression and emotional lability. As discussed in the next section, these reactions already are disclosed with specificity in the OxyContin labeling.

<sup>51</sup> *Adverse Reactions Section Guidance*, at 1.

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provide meaningful risk information to prescribing physicians with the caution to avoid cluttering the labeling with minor or speculative risks. As FDA has observed, “labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to ‘lose its significance.’”<sup>52</sup> In this case, given the factors noted above, the inclusion of risks such as “dysphoria” on the labeling could actually undermine the safety of OxyContin by detracting from the communication of more common and more significant risks listed in the labeling.

**C. The OxyContin Labeling Adequately Communicates the Risks of Dysphoria-Like Symptoms Even Though It Does Not Use the Term “Dysphoria”.**

The term “dysphoria” is a general term commonly used to describe a general sense of physical or mental discomfort. Stedman’s Medical Dictionary defines “dysphoria” as a “mood of general dissatisfaction, restlessness, depression, and anxiety; a feeling of unpleasantness or discomfort.”<sup>53</sup> Similarly, Dorland’s Medical Dictionary defines the term as “disquiet; restlessness; malaise.”<sup>54</sup>

Even though “dysphoria” is not listed as an adverse reaction on the OxyContin labeling, several of the more specific terms comprising the definition of dysphoria, or that are closely related to such terms, are included in the labeling. For example, the OxyContin labeling lists nervousness, anxiety, agitation, depression and emotional lability as observed adverse reactions.<sup>55</sup> Physicians reviewing the OxyContin labeling thus will not be hampered in their understanding of the dysphoria-like risks associated with the drug simply because it does not contain the specific term “dysphoria.”

FDA has advised that “[i]n characterizing overall adverse reaction experience, nonspecific terms that lack a commonly understood or precise meaning are discouraged, as use of such terms can be misleading.”<sup>56</sup> Therefore, when crafting the adverse reactions section of a drug’s label, companies are encouraged to avoid nonspecific terms in favor of terms with more precise and descriptive meanings. To that end, the Adverse Reactions section of the OxyContin labeling includes more specific, and arguably more meaningful, terms to describe reactions that may fall under the general “dysphoria” label.

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<sup>52</sup> 71 Fed. Reg. at 3922, 3935 (Jan. 24, 2006) (quoting 44 Fed. Reg. 37,434, 37,447 (June 26, 1979)).

<sup>53</sup> Stedman’s Medical Dictionary (27th ed. 2003).

<sup>54</sup> Dorland’s Medical Dictionary for Healthcare Consumers (31st ed. 2007).

<sup>55</sup> See Package Insert at 18-19.

<sup>56</sup> *Adverse Reactions Section Guidance*, at 9.

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**D. The Petition Fails to Provide Sufficient Evidence Justifying the Addition of “Dysphoria” as an Adverse Reaction.**

The Petition contends that dysphoria should be added to the current OxyContin labeling because, among other reasons, it was included as a “frequent adverse experience” in early preliminary drafts of the labeling.<sup>57</sup> The final draft submitted to and approved by FDA, however, did not include dysphoria as an adverse experience. It is unclear why preliminary drafts identified dysphoria as an adverse experience. Petitioner correctly notes that Purdue identifies dysphoria as an adverse experience in the labeling of its immediate-release oxycodone product, and Purdue used the labeling of that product (in addition to the labeling of MS Contin, which also includes dysphoria) as a starting point for early drafts of the OxyContin labeling.

The content of those early, preliminary drafts, however, is irrelevant. As noted above, dysphoria was not reported in the clinical study reports for the clinical trials supporting the approval of OxyContin. Thus, whether or not it was included in early, preliminary drafts, there was no strong, scientific basis for including dysphoria in the final version of the package insert submitted to FDA (nor, for that matter, in the current version of the labeling). Because the Petition provides no evidence that “dysphoria” should be listed as an adverse reaction, the Petition should be denied.

**V. The Petition Fails to Provide Sufficient Evidence to Support the Requested Labeling Change Revising the Boxed Warning.**

The Petition requests that FDA require Purdue to add the following language to OxyContin’s boxed warning:

OxyContin blood plasma levels peak and trough at levels similar to immediate release opioids of similar mg. strengths. There is no clinical evidence that OxyContin causes less euphoria and dysphoria than immediate release opioids and Purdue Pharma has received reports of euphoria associated with the use of OxyContin. OxyContin tablets are subject to abuse, misuse and diversion.<sup>58</sup>

As noted above, a boxed warning is “the most serious warning placed in the labeling of a prescription medication.”<sup>59</sup> Consequently, it is reserved for “[c]ertain contraindications or

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<sup>57</sup> See Petition at 14.

<sup>58</sup> *Id.* at 3.

<sup>59</sup> FDA Response to Connecticut at 2.

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serious warnings, particularly those that may lead to death or serious injury.”<sup>60</sup> Moreover, it typically must be based on clinical data or, in rare cases, animal data.<sup>61</sup>

The boxed warning language requested by Petitioner fails to meet these rigorous standards and would, in fact, detract from the important risks currently communicated in the existing OxyContin boxed warning. First, most of the language proposed by Petitioner relates to pharmacokinetic data, particularly comparative data between OxyContin and immediate-release oxycodone. While this information is important, it already is adequately communicated in the Pharmacokinetics section of the labeling and does not rise to the level of a “contraindication or serious warning” warranting placement in a boxed warning.

Second, the requested language comparing the rates of euphoria and dysphoria between OxyContin and immediate-release oxycodone is based not upon any clinical data (or even animal data), but solely upon a *lack* of such data. Boxed warnings typically should be based on clinical data or, in rare cases, animal testing data.<sup>62</sup>

Moreover, it is not appropriate to highlight information about adverse reactions in a boxed warning when, as with euphoria and dysphoria, they do not rise to the level of the risks being highlighted in the boxed warning and do not significantly aid in understanding those risks. The boxed warning for OxyContin is focused on the abuse liability of the product and provides strong warnings about the risk of “abuse, misuse and diversion.” Indeed, the boxed warning states that “[o]xycodone can be abused in a manner similar to other opioid agonists, legal or illicit,” and that this should be considered if the drug is prescribed or dispensed in situations where there is a concern about “misuse, abuse, or diversion.”<sup>63</sup> The language suggested by Petitioner adds nothing to the current warning.

Because the language proposed by Petitioner does not communicate information about serious risks beyond those already addressed in the boxed warning, it would most likely detract from the message already contained in that warning. Accordingly, Petitioner’s request should be denied.

**VI. The Petition Fails to Satisfy the Rigorous Requirements of Section 505(o)(4) Governing the Issuance of Safety Labeling Change Orders.**

The Petition requests FDA to “revoke its approval” of the current package insert for OxyContin and to “require” and “order” Purdue to make a number of safety-related labeling

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<sup>60</sup> 21 C.F.R. §201.57(c)(1).

<sup>61</sup> *Id.*

<sup>62</sup> *Id.*

<sup>63</sup> Package Insert at 1.

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changes, including: (1) removing the “log scale graph” set forth in the pharmacokinetics section of the labeling, (ii) disclosing dysphoria as an adverse experience, and (iii) more prominently disclosing the adverse risks of euphoria and dysphoria in a black box warning.<sup>64</sup> Although Petitioner’s request for FDA to revoke its approval of the drug’s labeling could be read as a request for FDA to withdraw approval of the NDA itself, Purdue does not interpret Petitioner’s demand so expansively.<sup>65</sup> Instead, the Petition seems to be limited to requesting that FDA “order” Purdue to make certain safety-related labeling revisions.

Although FDA has express authority to order companies to make safety labeling changes in certain circumstances, Petitioner’s request does not meet the applicable statutory standards. In particular, the Petition fails to identify any “new safety information” regarding a serious risk associated with the use of OxyContin that is not already included in the drug’s FDA-approved labeling.

The Food and Drug Administration Amendments Act of 2007 (“FDAAA”) granted FDA explicit authority to order NDA holders to make “safety labeling changes” in certain circumstances.<sup>66</sup> Under the statute, FDA is authorized to invoke this authority only if it becomes aware of “new safety information” that it believes should be included in the labeling of a drug. The term “new safety information” is defined as information derived from a clinical trial, adverse event report, post-approval study, peer-reviewed biomedical literature or active surveillance or other scientific data deemed appropriate by FDA about a *serious risk* or *unexpected serious risk* associated with use of the drug that the agency has become aware of since the drug was approved, a risk evaluation and mitigation strategy (REMS) was required or the last assessment of the REMS.<sup>67</sup> A “serious risk,” in turn, is defined as the risk of an adverse drug experience that results in death (or places the patient at immediate risk of death), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or an adverse experience that may jeopardize the patient and may require a medical or surgical intervention to prevent one of the above outcomes.<sup>68</sup>

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<sup>64</sup> Petition at 1.

<sup>65</sup> In the event the Petition is, in fact, requesting withdrawal of OxyContin’s NDA, FDA must provide Purdue with due notice and an opportunity for a hearing before taking the requested action. 21 U.S.C. §355(e); 21 C.F.R. §§314.150, 314.200. Purdue hereby notifies FDA that it does not waive these due process rights.

<sup>66</sup> 21 U.S.C. §355(o)(4).

<sup>67</sup> 21 U.S.C. §§355(o)(2)(C), 355-1(b)(3)(A). “New safety information” also includes information derived from the listed sources about the effectiveness of the approved REMS for the drug since the last assessment of the REMS. *Id.* §355-1(b)(3)(B).

<sup>68</sup> *Id.* §355-1(b)(4)-(5). An “unexpected serious risk” is defined as “a serious adverse drug experience that is not listed in the labeling of a drug, or that may be symptomatically and pathophysiologically related to an adverse drug experience identified in the labeling, but differs from such adverse drug experience because of greater severity, specificity, or prevalence.” *Id.* §355-1(b)(8).

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The Petition fails to satisfy these rigorous statutory requirements because it identifies no “new safety information” that would justify issuance of a safety labeling order. Indeed, the Petition does not identify any evidence from a clinical trial, adverse event report, post-approval study, peer-reviewed biomedical literature or other form of scientific data, as required by the statute, regarding a safety issue relevant to the Petition, such as the abuse liability of OxyContin or the adverse event dysphoria. Instead, the Petition relies almost exclusively on a rehash of events occurring prior to 2001 – approximately eight years ago – regarding unrelated marketing activities for OxyContin.<sup>69</sup> These events, however, are not relevant to the package insert itself (particularly the current version of the package insert), are not the type of scientific information envisioned by the statute, and, in any event, are not “new.” Although the Petition makes vague assertions about more recent information allegedly obtained by Purdue regarding physician comprehension of the semi-log scale graph, these unsubstantiated and non-specific allegations likewise fail to satisfy the standard of “new safety information.”<sup>70</sup>

The lack of any new safety information is particularly apparent with respect to the Petition’s request to add “dysphoria” as an adverse event. This request is based on nothing more than (a) Petitioner’s contention that early, preliminary drafts of the OxyContin labeling identified dysphoria as a frequent adverse event, (b) the fact that immediate-release oxycodone products list dysphoria as an adverse event, and (c) vague allegations that Purdue learned in 2007 that “physicians place significance on the adverse experiences of euphoria and dysphoria when evaluating the addictive potential of a drug.”<sup>71</sup> What is lacking is any solid scientific basis – particularly new scientific information – that would justify adding dysphoria to the Adverse Reactions section of the package insert.

Moreover, neither dysphoria nor euphoria are the types of “serious risks” to which FDA’s labeling authority applies. While both events may be troubling or disconcerting to patients who experience them, the adverse events typically are transient and do not result in death,

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<sup>69</sup> The Petition contains allegations of inappropriate marketing of OxyContin by certain Purdue supervisors and employees that were the subject of Purdue’s 2007 plea agreement regarding OxyContin. These facts, which all occurred prior to 2001, are not relevant to the issues raised in the Petition regarding the adequacy of OxyContin’s current FDA-approved package insert and, in any event, are well-known to FDA. Consequently, Purdue will not address these irrelevant, historical issues in its response to the Petition.

<sup>70</sup> The Petition’s allegations regarding the information supposedly obtained by Purdue in 2007 and 2008 are vague. Neither FDA nor Purdue should be forced to speculate as to the nature of the information described nor accept the Petition’s characterization of that information. FDA regulations require that “[i]nformation referred to or relied upon in a [citizen petition] submission is to be included in full and may not be incorporated by reference . . .” 21 C.F.R. §10.20(c). In this case, the Petition fails to satisfy this basic FDA requirement. The Petition may be referring to a few depositions conducted in the course of a product liability lawsuit initiated by Petitioner and her counsel, Philip W. Thomas, in Mississippi. These isolated, anecdotal events do not, in Purdue’s view, raise serious questions about the accuracy or truthfulness of OxyContin’s approved labeling. Without additional details regarding the alleged information referred to in the Petition, it is not possible for Purdue to respond to the allegations substantively.

<sup>71</sup> Petition at 15.

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hospitalization, a significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or an adverse experience that may jeopardize the patient and may require a medical or surgical intervention to prevent one of the above outcomes. Accordingly, there is no legal basis to require that dysphoria be added to the labeling as an adverse reaction or that information about the rates of euphoria and dysphoria be added to the boxed warning.

Finally, although “abuse, misuse and diversion” may be considered to be “serious” risks, these risks have been known since OxyContin was approved in 1995 and are adequately reflected in the current version of the approved labeling, as discussed in Section II of these comments. For all of the reasons set forth in this section, the Petition is legally deficient and should be denied.

**VII. Conclusion.**

Although Purdue respectfully opposes the Petition as deficient on both factual and legal grounds, as set forth more fully above, Purdue stresses that it is fully committed to ensuring that OxyContin’s FDA-approved labeling is complete and accurate and contains all necessary directions and warnings to ensure the safe and effective use of OxyContin.

We appreciate the opportunity to respond to the Petition and thank you for your consideration of this response. Should you have any questions, please do not hesitate to contact us.

Respectfully submitted,



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Attachments