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Department of Health and Human Services
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COMMENTS ON CITIZEN PETITION
Docket # 2005P-0072

The undersigned, on behalf of Purdue Pharma L.P. ("Purdue"), holder of approved New Drug Application 20-553 for OxyContin[®] (oxycodone HCl controlled-release) Tablets, 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg ("OxyContin") and approved New Drug Application 21-044 for Palladone[™] (hydromorphone HCl extended-release) Capsules, 12 mg, 16 mg, 24 mg, and 32 mg ("Palladone") submits these Comments on the February 1, 2005 Citizen Petition filed by Barbara Van Rooyan and received by Dockets Management on February 17, 2005. For the reasons discussed below, this Petition should be denied.

I. Introduction

In December 1995 OxyContin[®] (oxycodone HCl controlled-release) Tablets were approved by the FDA. OxyContin is today indicated "for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." At all times since approval, "moderate to severe pain" has been an element in the OxyContin indication and the indication never has been limited to specific disease states or to some other special disease process.¹ Since 1995, more than 7,500,000 patients have been prescribed OxyContin by their health care professionals.

Palladone[™] (hydromorphone HCl extended-release) Capsules were approved by the FDA on September 24, 2004, subject to an extensive description of appropriate indication and usage, as follows:

¹ On the first package insert approved by the FDA in 1995, the indication stated: "OxyContin[™] tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." [N.B.: All cited material in this response will be provided in its entirety upon request.]

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“Palladone™ (hydromorphone HCl extended-release) Capsules are indicated for the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time (weeks or months) or longer. Palladone™ Capsules should only be used in patients who are already receiving opioid therapy, have demonstrated opioid tolerance, and who require a minimum daily dose of opiate medication equivalent to 12 mg of oral hydromorphone. Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, or at least 30 mg oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or an equianalgesic dose of another opioid, for a week or longer. Appropriate patients for treatment with Palladone include patients who require high doses of potent opioids on an around-the-clock basis to improve pain control, and patients who have difficulty attaining adequate analgesia with immediate-release opioid formulations.

“Palladone™ Capsules are NOT intended to be used:

- **as the first opioid product prescribed for a patient.**
- **in patients who require opioid analgesia for a short period of time.**
- **on an as needed basis (i.e., prn).**

“An evaluation of the appropriateness and adequacy of immediate-release opioids is advisable prior to initiating therapy with any modified-release opioid. Prescribers should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen, to opioids, in a plan of pain management such as outlined by the World Health Organization, the Agency for Health Research and Quality, the Federation of State Medical Boards Model Policy, or the American Pain Society.

“Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. Patients receiving opioids should be routinely monitored for signs of misuse, abuse, and addiction. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however these patients will require intensive monitoring for signs of misuse, abuse, or addiction.”² (emphasis, underscoring and bold-face, as in the original)

Palladone has been prescribed for thousands of patients since first introduced in January 2005.

² Package Insert, “Palladone™ (hydromorphone HCl extended-release) Capsules.

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The Petition contains four requests. Numbers one and two ask that both medicines be removed from the market until “chemically reformulated” by the manufacturer to a “drug of minimal abuse potential.” Requests numbered three and four, apparently made in the alternative to requests numbered one and two, ask that the labels for both products be changed to restrict their medical indications to “severe chronic pain from documented peripheral tissue disease processes.”

While the Petition’s objective of reducing the suffering associated with prescription drug abuse is laudable³, the actions proposed would fail to achieve that goal and, moreover, would have a grave negative impact on patients taking OxyContin and Palladone as medically necessary for the proper management of their pain.

According to the standards provided in 21 C.F.R. 314.150, withdrawal of approval for Palladone and OxyContin must be based on a finding that these products are either not safe or not effective for patients under the conditions of use for which they are approved, or that they are misbranded under the conditions of use prescribed in their labeling.

The Petition should be denied because:

1. The Petitioner offers no credible evidence to support the proposition that these approved drugs are either not safe or not effective for patients, or that they are misbranded under the conditions of use prescribed in their labeling;
2. To the contrary, much of the argument against both products is based not on their proper use by the patient population for whom they were intended, but on their claimed effect on individuals who take them without medical oversight for non-medical purposes;
3. The suggestion that a product being safely used as directed by patients be withdrawn pending re-formulation in order to protect abusers is inconsistent with sound public health policy; and
4. The actions requested would not have any likely meaningful positive impact on the overall problem of substance abuse in this country, but would potentially harm patients by limiting the therapeutic alternatives available to their health care professionals.

³ The means used to advance that objective – errors of fact and distortions of data – are considerably less laudable. The most important of these are addressed in the body of this response. Since it is unnecessary to correct each and every misstatement and distortion in order to respond to the substance of the Petition, no attempt will be made to do so.

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II. Response to requests one and two, to recall approval of OxyContin (and generic equivalents) and Palladone and remove them from the market “until chemically reformulated by manufacturer(s) to drug [sic] of minimal abuse potential.”

These requests would make safe and effective medicines unavailable to patients for whom they are properly prescribed by health care professionals while the medicines are being reformulated to protect non-patients against the consequences of substance abuse. As such they must be denied.

A. The Petitioner offers no credible evidence to support the proposition that these approved drugs are either not safe or not effective for patients.

The Petition makes the unsubstantiated claim: “Large numbers of accidental overdoses of patients legally prescribed OxyContin have also been documented.”⁴ This bare assertion, without any factual support, cannot justify the actions requested, especially when these actions would compromise patient care.

Petitioner’s assertion is similar to allegations involving OxyContin made in many of the more than 600 lawsuits filed against Purdue Pharma. In these cases, most of the plaintiffs have asserted that they became addicts or were otherwise injured as a result of being prescribed OxyContin to treat their pain. With respect to the plaintiffs whose claims Purdue has closely examined in discovery, however, Purdue has found, time after time, that the plaintiff was either not addicted, was not a patient with a legitimate medical need for the medicine or had a substance abuse disorder prior to using (and/or abusing) OxyContin.

To date, more than 300 of those cases have either been dismissed by the courts or withdrawn by the plaintiffs. In no case has a judgment been entered against Purdue, nor has Purdue paid any money to any plaintiff to settle or dismiss any claim.⁵

Many of the cases that have been dismissed or withdrawn also involved claims, as made by Petitioner, that Purdue Pharma was untruthful in its marketing of OxyContin and that its marketing practices contributed to the plaintiffs’ injury. Such claims also have been addressed directly by the courts⁶ and it is instructive to review some of their findings.

⁴ A web site offered as the sole support for this claim is connected to a personal injury law firm and four current plaintiffs in active cases against Purdue Pharma, raising questions about the impartiality of the information on the web site and the web site’s reliability as the sole basis for Petitioner’s safety claims.

⁵ Although Purdue Pharma has paid nothing to settle any of the personal injury lawsuits involving OxyContin, in 2004, the company did settle (without an admission of wrong-doing) a consumer protection lawsuit brought by the West Virginia Attorney General.

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Judge Jennifer B. Coffman of the U. S. District Court for the Eastern District of Kentucky, in an order dated December 27, 2001, denied plaintiffs' motion in Foister, et al. v. Purdue Pharma L.P., et al. that sought to impose a variety of restrictions on access to OxyContin, even by patients with legitimate medical need who had valid prescriptions from a physician. Following an evidentiary hearing on the motion, during which Judge Coffman took testimony under oath from plaintiffs' witnesses, the Court, in a 14-page order and decision, said:

“The plaintiffs have failed to produce any evidence showing that the defendants' marketing, promotional, or distribution practices have ever caused even one tablet of OxyContin to be inappropriately prescribed or diverted.”

⁶ One court referenced by Petitioner, however, did not address either the safety or efficacy of OxyContin or, for that matter, of Palladone. Nor did its decision relate in any way to Purdue's marketing.

Petitioner notes a decision by Judge Sidney Stein of the United States District Court for the Southern District of New York, misstating its findings and suggesting that the patent issue in litigation had some bearing on the approval of OxyContin by the FDA. The false impressions thereby created in Petitioner's reference must be addressed.

The Endo opinion involved a patent granted by the U. S. Patent and Trademark Office (PTO), a process unrelated to the safety and efficacy issues presented by a New Drug Application (NDA) before the FDA, which requires support of all claims by adequate scientific grounds. The FDA approved Purdue's NDA for OxyContin based on its own independent review of Purdue's scientific claims using its own highly trained cadre of physicians and scientists. No part of the FDA approval process depends on the enforceability of its patents or statements made to the PTO. The two application processes are completely separate.

Moreover, there was no finding that “the representations made by Purdue to the government concerning the effectiveness of OxyContin for chronic pain sufferers were fraudulent and misleading.” Judge Stein's finding of “inequitable conduct” is based on the fact that, while Purdue's patent application stated that Purdue had discovered that about a four-fold range of dosages of the OxyContin formulation would treat about 90% of patients in pain, the company did not have experimental data to establish this statement at the time the patent application was filed in the PTO.

Judge Stein, in fact, found the claim itself to be true. The issue of the existence of studies, therefore, did not relate to claims actually made in the FDA application, but to inferences drawn by the Judge about the timing of studies related to a statement made in the patent application. No claim regarding the 90% effectiveness rate within a four-fold dosage range was asserted by Purdue to the FDA and no such claim appears in any OxyContin labeling or marketing materials.

In summary, the Endo patent opinion:

- takes no issue with the overall safety or efficacy of OxyContin;
- has no bearing on whether or not OxyContin is effective in treating moderate to severe pain; and
- has nothing to do with abuse, diversion, addiction, side effects, withdrawal, or overdose – or any other issue raised in this Petition.

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Similarly, in August 2002, the first state court to decide an OxyContin-based lawsuit on its merits dismissed the claims of a West Virginia plaintiff against Purdue. Relying on “the established legal principle that a plaintiff cannot recover when his own unlawful or immoral act caused the injuries in question,” Judge James J. Rowe, Chief Judge of the Eleventh Judicial Circuit, Greenbrier County, West Virginia decided the lawsuit brought by Brian Allen, as administrator of the estate of his deceased spouse, Rebecca Ann Allen, in Purdue Pharma’s favor.

In the seven-page written Order deciding Allen v. Purdue Pharma L.P., et al, Judge Rowe held:

“[The] Plaintiff and Mrs. Allen circumvented all safety measures set forth by Defendant in the form of warnings...[T]he use of OxyContin in contravention of those safety measures was the proximate cause of Mrs. Allen’s death.”

The Judge also noted:

“The undisputed evidence shows that OxyContin is currently and always has been a Schedule II drug, subject to the strictest regulation available. In fact, OxyContin can only be prescribed by a physician who is licensed by the Drug Enforcement Agency.”

“[T]he various warnings” provided by Purdue Pharma “clearly laid out the possibility that [the plaintiff’s] actions could lead to a fatal overdose...” Judge Rowe added.

Federal District Court Judge Danny C. Reeves agreed. In dismissing the claims of 8 plaintiffs against Purdue Pharma on summary judgment, he noted:

“Thus, OxyContin’s insert clearly set forth the potential dangers of the drug and the best manner in which to minimize those dangers.”⁷

The unsubstantiated claims made by Petitioner with respect to patient injury from OxyContin also are similar to those made in a front page series of newspaper articles published in October 2003 by the Orlando Sentinel.⁸

⁷ Foister v. Purdue Pharma, L.P., at al, Memorandum Opinion and Order Granting Defendant Purdue Pharma’s Motion for Summary Judgment, USDC, Eastern District of Kentucky, London Division, December 30, 2003, p. 27.

⁸ The October 2003 newspaper stories in turn gave rise to a hearing by the House Subcommittee on Criminal Justice, Drug Policy and Human Resources, selective portions of which are referenced at p. 5-6 by Petitioner. (See Section IV of this response for additional excerpts from the hearing that contradict the premise of this petition that restricting access to OxyContin and Palladone will somehow correct the problem of substance abuse in this country.)

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The Orlando Sentinel series was so fraught with errors and distortions that the paper ran four subsequent corrections, the last of which appeared on the front page of the Sunday edition on August 4, 2004. The correction stated that the October 2003 series:

“created the misleading impression that most oxycodone overdoses resulted from patients’ taking the drug to relieve pain from medical conditions...many of the victims were clearly drug abusers using illegal drugs along with oxycodone...”

and

“used a key statistic incorrectly and overstated the number of overdoses caused solely by oxycodone, the active ingredient in OxyContin and other prescription painkillers.”

Commenting on the Sentinel series’ linking of OxyContin to so-called “accidental” addiction by patients, the newspaper’s Public Editor said, “The extraordinary correction on Page A1 today makes clear how far off the mark that series was.”

In support of its claims of patient injury, the Petition mentions a report of the Government Accountability Office (GAO), presumably a reference to GAO-04-110, Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem, December 2003.

This report was the culmination of a two-year study by the GAO to determine how OxyContin Tablets were marketed and promoted, what factors contributed to the abuse and illegal trafficking of the product, and what actions Purdue Pharma and others have taken to address the problem.

After its two-year investigation, the GAO did not establish a correlation between Purdue Pharma's marketing strategies for OxyContin and its abuse. The GAO stated “... we could not assess the relationship between the growth in OxyContin prescriptions or increased availability with the drug’s abuse and diversion...” (p.29).⁹ None of the several factors that the GAO concluded might have contributed to the abuse and diversion of OxyContin included Purdue Pharma’s marketing or promotion of the product.

⁹ The GAO report also supports the points made in this response in Section IV, *infra*, that the problem of substance abuse did not originate with OxyContin and will not be solved by removing OxyContin, changing its indication or reformulating it to make it more abuse resistant. The report states, “[T]he Appalachian region, which encompasses parts of Kentucky, Tennessee, Virginia, and West Virginia has been severely impacted by prescription drug abuse, particularly pain relievers, including oxycodone, for many years. Three of the four states - Kentucky, Virginia and West Virginia - were among the initial states to report OxyContin abuse and diversion. Historically, oxycodone, manufactured under brand names Percocet, Percodan and Tylox, was among the most diverted prescription drugs in Appalachia”(p.31). Since these are all generic drugs, they are not heavily marketed by their manufacturers. The GAO report also states, as will be developed more completely in Section IV, *infra*, that, according to the Drug Enforcement Administration, “...OxyContin has not been and is not now considered the most highly abused and diverted prescription drug on a national basis” (p.33).

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Published after the Orlando Sentinel series discussed previously, but before the paper published its retractions and corrections, the report erroneously relied on the Sentinel's reporting to support some of its observations about injuries resulting from OxyContin use.¹⁰

All of this is not to say that there are not risks associated with OxyContin or with Palladone. There are risks, these risks are real and their potential consequences may be serious or even fatal. As noted by Judge Rowe and Judge Reeves, however, they also are the subject of comprehensive and express warnings, such as the warnings provided on the package labeling for Palladone and OxyContin.

An important risk associated with OxyContin and Palladone, although to no greater degree than with any other C-II opioid, is the risk of addiction. Because addiction is a serious condition, it is the subject of clear warnings for the products at issue here.

The risk of addiction – like other risks associated with prescription medicines – must be balanced by a medical practitioner with the best interests of the individual patient.

The majority of qualified medical and scientific opinion supports the FDA's view that the risk of addiction in the individual patient must be balanced against the benefits opioid medications may provide. As the FDA permits Purdue to say in its OxyContin and Palladone package inserts to this day:

“Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.”

Experts in pain management affirm this statement. For example, Dr. Kathy Foley, a leading pain treatment expert, stated:

“By highlighting OxyContin's illegal use, we fail to educate the public about the role such analgesic drugs play in providing relief for millions of patients suffering from severe pain.... [T]he war on drugs must not become a war on patients....”¹¹

The FDA, in 2001, said:

“Concerns of addiction should not prevent patients with appropriate pain conditions from using OxyContin or other narcotics for pain relief.”¹²

¹⁰ GAO Report, p. 10.

¹¹ Kathy Foley, “Patients in Pain: Casualties of the war on drugs,” Ideas for an Open Society, vol. 2, no. 4 (Oct. 2002).

¹² FDA Center for Drug Evaluation and Research, OxyContin: Questions and Answers (2001).

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Withdrawing approval of OxyContin and Palladone, subject to the development of more abuse-resistant alternatives, therefore, is not warranted by the fact that these medicines can be made unsafe when altered or consumed in a manner directly contrary to the express written warnings provided on the FDA approved labeling. All prescription medications entail risk. The requirement of a prescription prior to dispensing is intended to minimize that risk through (1) proper patient selection by a health care professional and (2) medically supervised use by the intended patient. The actions of willful abusers should not be used to justify depriving a patient with legitimate medical need who is adhering to a treatment regimen of a prescribed medication.

B. The alternatives proposed by Petitioner would not provide the same clinical benefits as OxyContin and Palladone for many patients.

The United States recognizes in an international treaty that it has a duty to make effective opioid analgesics available to its citizens.¹³ The United States Congress has found and declared that opioid narcotics can have “a useful and legitimate medical purpose and are necessary to maintain the health and general welfare of the American people.”¹⁴ The controlled-Release (CR) formulations OxyContin and Palladone have been found to be safe and effective for their approved conditions of use and provide health care professionals in the United States with therapeutic options that are distinctive from those found in immediate release opioids. The availability of immediate release opioids does not provide a basis for withdrawing approval of CR formulations, as Petitioner suggests.¹⁵

The petitioner has incorrectly interpreted clinical studies of controlled-release (CR) hydromorphone and controlled-release oxycodone as showing no advantage for the controlled-release dosage forms.

The randomized, double-blind studies cited by the Petitioner¹⁶ compared equivalent daily doses of OxyContin given twice a day with immediate-release oxycodone given on a forced-

¹³ Preamble, Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol Amending the Single Convention on Narcotic Drugs.

¹⁴ 21 USC §801.

¹⁵ Cf., Notice of Proposal to Withdraw Approval of Two New Drug Applications and One Abbreviated New Drug Application (Terfenadine), 62 Fed. Reg. 9, p. 1889-1892, January 14, 1997.

¹⁶ Hale ME, Fleischmann R, Salzman R, Wild J, Iwan T et al. Efficacy and safety of controlled-release and immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. Clin. j Pain 1999 Sep; 15 (30 179-83; Kaplan R, Parris WC, Citron ML, et al. Comparison of controlled-release and Immediate-release and oxycodone tablets in cancer pain. J Clin Oncol. 1998 Oct; (10): 3230-7; Stambaugh JE, Reder RF, Stambaugh MD et al. Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled and immediate-release oral oxycodone in cancer pain patients. J. Clin Pharmacol. 2001 May; 41(5): 500-6.

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dose, fixed schedule every 6 hours. Similar studies, also cited by Petitioner, were done for a twice a day sustained-release formulation of hydromorphone compared with immediate-release hydromorphone given on an every 4 hour fixed dosing schedule.¹⁷ The NDA studies cited by the Petitioner were designed with a limited purpose, to show the safety and efficacy of the controlled-release product, as compared with an optimal fixed-schedule dosing of the immediate-release dosage form. These studies were not designed for, nor did they demonstrate, the significant therapeutic advantages for some patients of CR dosage forms over immediate release formulations.

The CR drugs were designed, labeled and recommended for use in patients where around-the-clock analgesia is needed for an extended period of time.¹⁸ Such patients seek continuous pain relief adequate to enable them to sleep, work, function in activities of daily living, and interact normally with family, friends and colleagues in the workplace. The therapeutic advantage for these dosage forms over immediate-release equivalents is that the patients and their caregivers *do not have to administer pain medications every few hours* to achieve adequate pain relief. The benefits are minimizing episodes of pain, minimizing medication administration and allowing patients to sleep through the night.¹⁹

Current analgesic guidelines recognize these facts and recommend long-acting opioids, either those with a long inherent half-life or those whose duration of action has been extended by putting the medicine into a modified-release formulation, supplemented with immediate-release agents for breakthrough or incident pain. MS Contin[®] (morphine sulfate controlled-release) Tablets, OxyContin and Palladone were developed to meet these well-defined clinical needs.²⁰

¹⁷ Hays H, Hagan N, Thirlwell M, et al. Comparative clinical efficacy and safety of immediate release and controlled release hydromorphone for chronic severe cancer pain. *Cancer*. 1994 Sep 15;74(6): 1808- 16; Bruera E, Sloan P, Mount B. A randomized, double-blind, double-dummy, over trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. Canadian Palliative Care Clinical Trials Group. *J Clin Oncol* 1996 May; 14(5): 1713-7.

¹⁸ OxyContin Package Insert, Black Boxed Warning, "OxyContin tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

¹⁹ American Geriatrics Society, AGS Panel on Persistent Pain in Older Persons, The Management of Persistent Pain in Older Persons, *JAGS*, 50; 5205-5224, 2002, page S216:

"Persistent pain is an exhausting experience; deconditioning, sleep deprivation, and poor nutrition commonly result from unrelieved pain. Most patients will cope better if drugs are prescribed to support exercise, enjoyable activities, and a good night's sleep..... Drug regimens for the older patients should be simplified as much as possible, and regimens should be adjusted to meet individual needs and life styles."

²⁰ American Pain Society, Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, page 29, American Pain Society, Glenview, IL.

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The same clinical needs are not met by immediate release products. The immediate release products noted by the Petitioner therefore do not constitute available alternative medicines of proven lesser risk such as would justify or otherwise support withdrawal of Palladone and OxyContin.

C. Pain patients should not be deprived of medicines during the extensive time period likely to be required for the development of abuse-resistant forms of pain medications.

Developing new forms of pain relievers that will be more resistant to abuse, while still providing safe and effective pain control to patients with pain, is a worthy, but complex scientific objective. The work is challenging, and it will take time to complete. State of the art pain management practices – and good patient care – should not be sacrificed while the work progresses.

Development of abuse-resistant pain medications is Purdue Pharma's number one research priority. The company has been working to develop such opioid medicines since 1996, long before reports of unexpected and widespread OxyContin abuse surfaced.

To date, Purdue has spent in excess of \$150 million to test and develop more abuse-resistant pain relievers and research projects concerning seven such products are currently underway. It has been publicly reported that 19 other companies are working on similar projects and that 450 patent applications have been issued since 1998 for ways to reduce the abuse potential of pain relieving medications.²¹ As these figures demonstrate, Purdue Pharma is aggressively pursuing – in vigorous competition with other companies – the development of abuse resistant medications, contrary to Petitioner's assertions.

Regrettably, none of this activity has produced a commercially available medication as described in the Petitioner's first and second requests and it is reasonable to conclude that no such medication is likely to be available for years to come. As a result, in these first and second requests, Petitioner essentially asks the FDA to deprive patients taking OxyContin and Palladone of their pain medications until such time as these medicines can be reformulated to better defeat the objectives of those who would abuse them.

“Controlled-release oral opioid preparations and transdermal opioid preparations are among the most important recent innovations in opioid analgesic treatment because their long duration of action lessens the severity of end-of-dose pain and often allows the patient to sleep through the night.”

American Geriatrics Society, AGS Panel on Persistent Pain in Older Persons, The Management of Persistent Pain in Older Persons, JAGS, 50; 5205-5224, 2002, page S217

“Long-acting or Sustained-Release analgesic preparations should be used for continuous pain.”

²¹ See, Kaufman, “Drug Firms Trying to Make Painkillers Less Abusable; Efforts Include More Tamper-Proof Pills and Compounds,” Washington Post, June 14, 2004.

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D. Even if there were a basis to remove OxyContin and Palladone from the market until chemically reformulated to drugs of minimal abuse potential (and there is no such basis), there would be no rational basis to limit such action to the two referenced products.

The Petitioner asserts that OxyContin and Palladone should be removed from the market in part because they have become or are likely to become substances of abuse. A similar rationale also would require removal of all morphine, hydrocodone, oxycodone, fentanyl and related opioid medications that are currently available and labeled to have significant abuse liability. Removal under this theory also would be required for all the various opioid analgesics listed in various data sources²² as being more frequently abused than OxyContin²³. Eventually, as abusers shifted their preferences from removed to remaining products, the theory advanced by the Petitioner would require the elimination of an entire class of medications, turning the clock on pain care back decades if not centuries.

• • • • •

Developing an abuse-resistant pain medication requires enormous investments, not only of money but also of time. Well it should. As a matter of sound public health policy, abuse-resistant medications pose special threats and risks. Abuse-resistant medications are not intended to protect patients who use them properly. They are intended to defeat the intentions of those who would abuse them. It would be ethically improper to create safety risks for adherent patient populations in order to protect abusers. While protection of abusers is a worthy objective, it is not one that should be accomplished at a sacrifice to patients.²⁴

²² See Section IV, below.

²³ Palladone also is not among the most abused opioid narcotics. It has been available since January 2005.

²⁴ This perspective is not unique to Purdue Pharma. Testifying before the Senate Committee on Health, Education, Labor and Pensions, Dr. John Jenkins, Director of the Office of New Drugs at the Food and Drug Administration, noted:

“The second thing that we all have to remember when we start adding a second active ingredient to a product, is that the legitimate patients who are taking the product don't need that second active ingredient. So, you have to be careful that that second active ingredient is not compromising the effectiveness of the Oxycodone, and also is not exposing them to an undue risk of adverse reactions. So, we're eagerly working with Purdue Pharma on those efforts at reformulation. I think they can be useful, but they will not solve the entire problem.”

Hearing, Committee on Health, Education, Labor and Pensions, Senate, 107th Congress, First Session, February 12, 2002, p. 19.

Dr. Michael Levy, Vice Chairman of Medical Oncology, Director of Supportive Oncology, and Director of the Pain Management Center at the Fox Chase Cancer, had earlier expressed the same view to another congressional committee:

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III. Response to requests three and four, to limit indications for OxyContin and Palladone to “severe chronic pain from documented peripheral tissue disease processes.”

Petitioner’s requests numbered three and four emanate from a false premise. OxyContin was never restricted, as Petitioner suggests, to the treatment of “cancer and other severe pain.” (Petition, p. 6) The first FDA-approved package insert for the product – included with the first product shipped from OxyContin manufacturers – plainly stated that OxyContin was indicated for the management of “moderate to severe pain,” without regard to a specific disease state or origin of pain. That portion of the indication has never changed, nor is there a scientific rationale for it to be changed now.

A. The “moderate to severe pain” part of the indications for OxyContin and Palladone is appropriate.

The indication for moderate to severe pain, when it is a chronic or persistent condition²⁵, describes conditions of pain that interfere with the patient’s ability to function normally in the activities of life. It does not include commonplace and ordinary aches and pains, or transient pain from pulled muscles, cramps, sprains, or similar discomfort. Patients suffering from moderate to severe pain are, in the first instance, entitled to relief and, in the second, certainly should not be deprived of that relief because the medications that may provide it are subject to abuse.

Advisors to the FDA have considered and the FDA itself has recently ratified the appropriateness of the “moderate to severe” part of the indications for long-acting opioids, including OxyContin.

“I would like to urge a note of caution that, you know...simple solutions to complex problems rarely work...So we have to do this professionally. We have to, you know, fix the problem, not the blame. We need to recognize that it isn’t that simple scientifically...And so it is not that easy to jump and find a magic bullet as much as we would like it. Attempts at mixed drugs, like Talwin, which were – and Nubain, which were part agonist, part antagonist, showed that they had a ceiling, they didn’t relieve severe pain, and they caused different side effects that made them worse than pure opioids so that the Agency for Healthcare Policy and Research says do not use them.”

Hearing, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives, 107th Congress, First Session, August 28, 2001, p. 74-75.

²⁵ Petitioner has addressed only a part of the indications for these medicines, an illogical approach that ignores other important factors in the package insert that are used by health care professionals in proper patient selection. While the discussion in response to the Petition will be restricted to the “moderate to severe” language, it will be set in the context of the approved indications for OxyContin and Palladone.

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During an FDA Anesthetic & Life Support Drugs Advisory Committee (ALSDAC) meeting on September 9, 2003, medical experts presented an overview of medical and scientific facts surrounding the under treatment of pain and the historical and appropriate use of opioid pain medications. These experts urged the FDA and the Advisory Committee to rely on these facts in their deliberations and warned against unnecessarily restricting the legitimate medical use of opioid medications.²⁶ The majority of the advisory panel members expressed an opinion that restricting modified-release opioid medications for use in severe pain only would be a disservice to millions of pain sufferers.

More recently, in response to an inquiry from Congressman Mark E. Souder, the FDA, through Amit K. Sachdev, Associate Commissioner for Legislation, reiterated and expanded on the position taken by its Advisory Panel. Congressman Souder's question and the FDA response are as follows:

"2. Does the number of conditions for which a drug is approved by FDA impact the illegal use of the drug? In other words, if the number of approved uses increases, does that increase the potential for the drug to be diverted or misused? Should drugs like OxyContin be approved for use in treating "moderate" or even lesser levels of pain?"

At the September 9 and 10, 2003, Advisory Committee meeting on issues of risk management for the controlled-release opiate drug products, witnesses presented testimony that suggests there is a correlation between how widely a drug is used and the potential for abuse and misuse of that drug.²⁷ The witnesses suggested that if a drug is very commonly prescribed and commonly used in many settings, it has a higher likelihood of abuse as a result of its wide use. There is not, however, a clear, close relationship between the number of approved uses for a drug and its level of distribution and usage in the community. Drugs with only a single indication may have very widespread use if that single indication is quite common (for example, a new statin drug for hypercholesterolemia may be widely used, due to the prevalence of the condition in the population). On the other hand, a drug that is indicated for treatment of a number of uncommon conditions (for example, rifampin, an antibiotic approved for treatment of tuberculosis and a number of other uncommon infections) may have quite limited usage. Pain is a very common condition in our society, affecting millions of patients, and the extent of use of a drug is driven by many factors beyond indications. The indication for OxyContin is for "the management of

²⁶ For more details on the health care professionals invited to testify on this subject, please see text of presentations made by Steven Passik, PhD and Arthur Lipman, PharmD at the FDA Advisory Committee meeting in September 2003 available at <http://www.fda.gov/ohrms/dockets/ac/cder03.html> - AnestheticLifeSupport (also see FDA Transcripts, Exhibits 7 and 8).

²⁷ September 2003 Advisory Committee Transcript -- DEA's Role in Risk Management of Opiate Analgesics: Terrance Woodworth, M.S. <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3978T1.htm>.

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moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." This indication not only bounds the appropriate severity of pain that a patient should have, but also sets other important parameters for the indicated use. For example, OxyContin is not appropriate, by this indication, for "as needed" use nor for short-term use, like after minor trauma or a dental extraction.

"FDA approved OxyContin for "moderate to severe" pain rather than just "severe" pain for several reasons. First, pain is not monotonic, and even in patients with chronic painful conditions, their pain tends to wax and wane. Patients with chronic pain may rate their pain as severe one day and only have more moderate levels on another. Further, it is clear from a number of scientific studies that if one looks at significant functional impairment as a threshold for defining significant pain (which is a subjective assessment), many patients with such dysfunction will only rate their pain as moderate or moderately severe, rather than severe. Therefore, patients with pain that importantly limits their daily activities may only rate their pain subjectively as moderate or moderately severe. The question of whether OxyContin and other potent opiates should be limited to severe pain only was posed to the Advisory Committee in the September 2003 meeting. The committee strongly recommended that FDA maintain the indication to include moderate pain. Misuse and abuse of a drug is not driven by FDA's approved indication. However, legitimate use in practice may be restricted (when formularies or practice guidelines require following labeled indications), thus negatively affecting the legitimate use of OxyContin."²⁸ (emphasis added)

Restricting the indications for OxyContin and Palladone, as proposed by Petitioner, would exacerbate an already severe public health problem in the United States. The National Institutes of Health (NIH), an Agency under the U.S. Department of Health and Human Services, regards itself as "the steward of medical and behavioral research for the Nation." NIH notes:

"There are more than 50 million Americans who experience chronic pain and more than half of dying patients experience moderate to severe pain during the last days of their life. Pain is a frequent cause for clinical visits with approximately 45% of the population seeking medical help for pain at some point in their lives. Pain is found across the lifespan and it has been estimated that four out of every ten people with moderate or severe pain do not get adequate relief.

"Pain is personal and subjective, is affected by mood and psychosocial factors, and demonstrates tremendous individual variation. Depression commonly complicates pain and adds to the disability and impairment found in disorders with chronic pain. Pain in combination with depression is a risk factor for suicide. Pain interferes with quality of

²⁸ Letter, Amit K. Sachdev, Associate Commissioner for Legislation, FDA, to The Honorable Mark E. Souder, April 26, 2004.

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life, sleep and productivity, and pain increases utilization of health care resources. However, many health care providers do not have the background to effectively treat pain.

“Pain is frequently undertreated by healthcare providers. For example, a survey of several hundred ambulatory AIDS patients found that fewer than 8% of patients reporting “severe” pain were prescribed a strong opioid such as morphine, despite published guidelines. Adjuvant analgesic drugs (e.g., antidepressants) were also prescribed to only a small fraction of these patients. Opioid analgesics are the accepted treatment for acute pain, cancer pain and pain at the end of life, and recently have been recommended for chronic, nonmalignant pain. Patients can be treated with this therapy without developing tolerance, addiction or toxicity. Nevertheless, health care providers continue to fear these adverse outcomes, and believe that opioid use may result in a downhill spiral of further disability, depression and pain, in spite of contrary evidence. A further barrier to chronic opioid therapy is the lack of a good objective measure to determine whether a person requesting increased opioid dosage is abusing opioids or is receiving insufficient benefit from therapy. This second scenario is so common in certain conditions (e.g., cancer, sickle cell disease) that the term “pseudo addiction,” has been used to describe the patient who is demonstrating drug-seeking behavior because his or her pain is undertreated.”²⁹

B. There is no sound medical or scientific rationale for a restriction on OxyContin and Palladone to use in the management of pain “from documented peripheral tissue disease process” and such a restriction would be inhumane.

Only patients suffering pain “from documented peripheral tissue disease process” would be able to receive OxyContin or Palladone were the Petition to be granted. Such a limitation would be fundamentally inconsistent with the accepted science of pain generation and the patient’s perception of and response to pain. If granted, it would needlessly deprive many pain patients – including patients suffering from cancer and post-cancer pain – of the medicines now chosen for them by their doctors.

First of all, there does not exist a commonly accepted medical definition of “peripheral tissue disease process.” Using this term in a medical indication for a C-II drug therefore would be more confusing – and therefore dangerous – than it would be helpful to practitioners seeking to identify proper patients for therapies that include Palladone or OxyContin.

The International Association for the Study of Pain defines pain as: “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.”³⁰ The IASP further states:

²⁹ <http://grants1.nih.gov/grants/guide/pa-files/PA-01-115.html>, accessed 4/21/05.

³⁰ IASP Pain Terminology, accessed on April 25, 2005 at 0820 EDT from: <http://www.iasp-pain.org/terms-p.html#Pain>

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“Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.”

The standard of “documented” also is inconsistent with the realities of medical practice and therefore potentially detrimental to patient care. In some cases, but certainly not all, there can be evidence of an injury to or disease process affecting peripheral tissue (e.g., a second-degree burn, EMG evidence of diabetic peripheral neuropathy, an osteosarcoma of the femur). Since there is no test – whether medical or psychological – that can unequivocally document the presence or absence of pain or, if it is present, its severity, the documentation requirement proposed in the Petition would virtually preclude the use of these medicines for the treatment of pain.

The limitation Petitioner envisions to “peripheral tissue disease” is untenable, based on medical science. Many painful conditions arise in non-peripheral tissues, such as post-polio syndrome, post-stroke pain, arachnoiditis, spinal cord tumors, syringomyelia, and phantom limb pain, all of which occur within the central nervous system, which is, by anatomic definition, not peripheral.³¹ Likewise, most physicians do not consider internal organs to be “peripheral tissue,” yet tumors and inflammatory bowel disease, to name but two conditions, frequently cause pain of the type for which modified-release opioids may be one therapeutic consideration.

The indication for OxyContin has always included the treatment of moderate to severe pain whether the cause of the pain is cancer or from some other disease process. The concept of pain as a “disease unto itself” is derived from the well-documented changes that occur in the nervous system when pain is untreated or undertreated. These changes can become permanent, resulting in pain generators that may persist even after the underlying disease process causing the original pain has been treated.

The recognition by the Petitioner of centrally mediated pain is significant since this type of pain can be moderate to severe, and can be extremely debilitating to the patients who have it. There are numerous approaches to the treatment of centrally mediated pain, including opioid medications, which may be effective in some cases. The Petitioner states that opioids have

³¹ Tasker RR. *Central Pain States* (Chapter 23), in *Bonica's Management of Pain*, 3rd ed., Loeser JD, Butler SH, Chapman CR, Turk DC (eds), Lippincott Williams & Wilkins, Philadelphia. 2001. Boivie J. *Central Pain* (Chapter 38), in *Textbook of Pain*, 4th ed., and Beric A. *Spinal cord damage: injury* (Chapter 39), in Wall PD, Melzack R (eds), Churchill Livingstone, Edinburgh. 1991.

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adverse effects on brain chemistry. All drugs that act in the central nervous system affect the functioning of the brain by altering receptor activity, neurotransmission and other aspects of brain function. These effects can reduce symptoms of disease and improve a patient's well being. As stated in the response to a previous allegation of the Petitioner, there are known adverse effects on the central nervous system from under treated or untreated pain, which can be attenuated by the appropriate treatment of pain with opioids and other modalities.

C. The risk management programs developed for OxyContin and Palladone are the most comprehensive data gathering mechanisms currently available for use in attempting to curb future abuse of these products while not interfering with appropriate patient access to them.

Risk management, according to the FDA Guidances, begins with risk assessment. The risks of modified-release opioid analgesics involve four distinct populations: intended patients, children (accidental exposure), abusers (spanning the spectrum from first time, experimentation to addiction), and the criminals who supply the abusers illicitly. Purdue has put together a comprehensive risk management program that includes risk assessment (in clinical trials); surveillance for indicators of diversion, abuse and addiction; mapping of these indicators to geographically specific areas; deployment of risk minimization actions specific to the particular findings in a local area; and follow-up to assess the outcome of such interventions. An External Advisory Board of experts in the study of various aspects of drug abuse advises Purdue on the risk management program. The risk management programs for both OxyContin and Palladone have been reviewed by and discussed extensively with the appropriate offices within the FDA and were the subject of the FDA Analgesic and Life Support Drugs Advisory Committee (ALSDAC) meeting referenced previously in this document. The studies that form the backbone of the surveillance system are all done by principal investigators at independent universities or research companies. To date, the conclusions of these investigators, as presented at numerous scientific meetings, include the following:

- Abusers of a given prescription opioid are similar to abusers of other prescription opioids.
- Abuse of prescription opioids is typically seen in those with a history of abuse of multiple drugs, both licit and illicit.

The RMPs for OxyContin and Palladone are as extensive as any currently in effect for medicines containing controlled substances. Hopefully, they will have the impacts with respect to these products described above, but their potential benefits should not be over-estimated. No RMP for a single product will succeed in overcoming what the data clearly demonstrate to be the longer standing and more pervasive problem of substance abuse in the United States.

IV. Overview: Providing for Patient Needs while Controlling Substance Abuse

As noted at the outset of this response, we support Petitioner's objective to reduce the suffering associated with prescription drug abuse. By focusing on two prescription medications, however, the Petition has failed to identify the true nature of the problem. As a result, the solution it proposes would not impact the very real problem of substance abuse, but would merely shift abuse to those medicines that remained on the market, while jeopardizing the medical care of pain sufferers who properly use and benefit from the use of OxyContin or Palladone.

Abuse of prescription drugs, and of OxyContin in particular, is a consequence – not a cause – of a rising incidence of substance abuse in America. Data from the Drug Abuse Warning Network (DAWN) show a 6.4% increase in the number of Emergency Department (ED) mentions for all major substances of abuse between 1994 and 1996 (from 449,964 to 478,676); and a 5.4% increase for "narcotic analgesics/combinations" during that same time period (from 44,518 mentions to 46,941 mentions).³² Data from the National Household Survey on Drug Abuse (NHSDA) show that the incidence of new nonmedical users of psychotherapeutics (stimulants, sedatives, and pain relievers) was rising steadily prior to 1996, beginning in the mid-1980s. The number of nonmedical initiates of opioid analgesics rose from 400,000 (mid-1980s) to approximately 1 million in 1995. Alcohol incidence was also rising steadily beginning in 1989 and, between 1990 and 1996, the estimated annual number of new marijuana users increased steadily from 1.4 million to 2.5 million.³³ All of these data show a pervasive increase in substance abuse antedating the introduction of either OxyContin (first full year, 1996) or Palladone (2005) into the marketplace. The problem of substance abuse in general is real, as is the problem of prescription drug abuse in particular, but it is a "substance abuse" problem, not limited to OxyContin or Palladone and not remediated by limiting patient access to these medicines or eliminating them altogether.

In fact, while the abuse of OxyContin is a problem that Purdue Pharma takes with the utmost seriousness, no federal database or study has ever listed OxyContin – or oxycodone for that matter – as the most abused prescription pain medicine. The recently released 2003 National Survey on Drug Use and Health (formerly, the NHSDA) assessed "lifetime non-medical use" of selected pain relievers. Results showed the 8.3% of individuals 12 years of age or older reported having ever used "Darvocet, Darvon or Tylenol with Codeine" nonmedically, and 6.6% reported ever using hydrocodone-containing "Vicodin, Lortab or Lorcet" nonmedically compared to the

³² Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Emergency Department Trends from the Drug Abuse Warning Network, Final Estimates 1994-2001, DAWN Series D-21, DHHS Publication No. (SMA) 02-3635, Rockville, MD, 2002. Table 2.2.0, p. T-18.

³³ Substance Abuse and Mental Health Services Administration. (2002). *Results from the 2001 National Household Survey on Drug Abuse: Volume I. Summary of National Findings.* (Office of Applied Studies, NHSDA Series H-17, DHHS Publication No. SMA 02-3758). Rockville, MD. p. 44-48.

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1.2% who reported having done so with OxyContin. Similarly, the federal DAWN 2002 report on drug abuse-related Emergency Department visits shows that, since 1996, hydrocodone combination products (Vicodin, Lorcet and generics) have been consistently mentioned as drugs of abuse more frequently than oxycodone.³⁴

All of the analgesic drugs are involved, with drugs containing oxycodone (including OxyContin) and hydrocodone-containing drugs present as significant drugs of abuse, but as part of – not all of – the problem.³⁵

³⁴ Substance Abuse and Mental Health Services Administration, Office of Applied Studies, National Survey on Drug Use and Health, 2002 and 2003, Table 1.129B, p. 40603, <http://www.drugabusestatistics.samhsa.gov/nsduh.htm#NSDUHinfo>; Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Emergency Department Trends from the Drug Abuse Warning Network, Final Estimates 1995-2002, DAWN Series D-24, DHHS Publication No. (SMA) 03-3780, Rockville, MD, 2003. Table 2.8.0, p. T-98.

In discussing diversion, Petitioner claims “OxyContin (and soon Palladone) are easily available through Internet pharmacies. Although many rogue Internet pharmacy sites intensively advertise the availability of OxyContin, Purdue has consistently been told by several law enforcement agencies that they’ve been unable to actually purchase the medication, or a counterfeit facsimile, via the Internet. In several instances where media reports alleged OxyContin was obtained via the Internet, Purdue has contacted the reporters and law enforcement officials involved and determined that these claims were not true. This information is accurate to the best of Purdue Pharma’s knowledge as of April 15, 2005.

³⁵ In dealing with the problem of substance abuse, it is particularly unhelpful to use data as deceptively as they are used in the Petition. For example, it is not true, as Petitioner claims, that “...nonmedical use of prescription painkillers now comprises 30% of all emergency room visits.” In truth, according to the last full year of DAWN data (2002), ED visits (or “episodes” in DAWN) for adverse health consequences of abuse of prescription opioids represented ~ 0.06% of all ED visits nationally and *mentions* of prescription opioids represented 9.85% of all ED mentions reported to DAWN in 2002.

There also is no support from any recognized database for Petitioner’s claim that there has been a 49% increase in OxyContin abuse during the past four years. The report she cites, *Monitoring the Future: National Results on Adolescent Drug Use: Overview of Key Findings, 2004*. (NIH Publication No. 05-5726). Bethesda, MD: National Institute on Drug Abuse, did not begin collecting data on OxyContin until 2002. For the most recent two years, the authors of that report actually state: “*OxyContin...showed some evidence of increased use in 2003 in all grades, and in 2004 among 12th graders, though none of the increases reached statistical significance*” Citation: Johnston, L.D., O’Malley, P.M., Bachman, J.G., & Schulenberg, J.E. (2005). *Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings, 2004*. (NIH Publication No. 05-5726). Bethesda, MD: National Institute on Drug Abuse, p. 5. The DAWN system underwent major changes in 2003. As a result, “DAWN data and estimates for 2003 [and onwards] are not comparable to those for any prior years.” Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Drug Abuse Warning Network, 2003: *Interim National Estimates of Drug-Related Emergency Department Visits*. DAWN Series D-26, DHHS Publication No. (SMA) 04-3972. Rockville, MD, 2004, p. 7. Similarly, the National Survey on Drug Use and Health (NSDUH) changed its methods for collecting and reporting data in 2002 and therefore warns: “[E]stimates from the 2002 and 2003 NSDUHs should not be compared with estimates from the 2001 and earlier NHSDAs to assess changes in substance use over time.” p. 1, Substance Abuse and Mental Health Services Administration. (2004). *Overview of Findings from the 2003 National Survey on Drug Use and Health* (Office of Applied Studies, NSDUH Series H-24, DHHS Publication N. SMA 04-3963). Rockville, MD, p. 1.

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None of the preceding is intended to suggest that abuse of OxyContin is not a serious problem in a number of communities. However, it is very clear from these data that abuse of OxyContin is not the problem upon which national health policy in the area of substance abuse or prescription drug abuse and diversion should focus. Instead, abuse of OxyContin is part of the larger problem of prescription drug abuse in the United States, which is in turn part of the still larger problem of drug and substance abuse generally.

Eliminating OxyContin or Palladone will not make the much larger problem of substance abuse go away, but will merely shift the drugs, licit and illicit, sought by the abuser.

This was the same conclusion reached by the DEA's Special Agent in Charge, Miami Division, when questioned by dentist and Congressman Charles Norwood at the February 4, 2004 hearing in Florida of the United States House of Representatives Subcommittee on Criminal Justice, Drug Policy and Human Resources. While Petitioner cites this hearing in support of the request that OxyContin and Palladone be withdrawn from the market until abuse resistant formulations are available, the Petition fails to mention the following colloquy:

Dr. Norwood. I have just one statement and I would like to know if you guys agree with it. Heroin is illegal in Florida, but heroin is your No. 1 problem. If we were to make the manufacture of OxyContin illegal, it would still be a problem, it

Likewise, references to the 2002 DEA report about OxyContin related deaths is misleading. The DEA report did not address the cause of death based on the medical examiner reports collected. It assumed that OxyContin was the only source of the oxycodone found in blood tests reported by medical examiners. It further assumed that the detection of oxycodone postmortem, without a concomitant report of aspirin or acetaminophen, was evidence that OxyContin was the sole source of the oxycodone. This assumption is flawed for a number of reasons, to wit: many toxicology labs do not routinely run tests for aspirin or acetaminophen on postmortem samples unless there is an implication from the requesting medical examiner that either of these drugs are important to detect and quantify; those labs that do routinely test for these drugs often do not report the results unless they are outside of their usual therapeutic ranges and, therefore, could have ramifications in the opinion regarding cause or manner of death; and, even if no additional analgesic is detected postmortem, the assumption that the source of oxycodone is solely from OxyContin is unsupportable, even if OxyContin was found at the scene or in the decedent (in the form of tablets or fragments thereof), as there are a number of other single entity oxycodone formulations on the US market which, according to information from the RADARS[®] System, are abused and diverted to about the same degree as is OxyContin. The only peer-reviewed study to assess the cause of death in cases where oxycodone was present in the decedent's blood stream was published in Journal of Analytical Toxicology (JAT) in 2003. The JAT study found that the vast majority of drug abuse deaths involving oxycodone (96.7%, or 889 of 1014 drug abuse deaths) are related to the ingestion of multiple drugs (an average of 4.5 drugs per decedent), not solely oxycodone (3.3%, or 30 of 1014 drug abuse deaths). This data, assimilated from autopsies performed in 23 states, is inconsistent with Petitioner's implicit assertion that abuse of OxyContin is the problem, as opposed to the abuse of prescription medications, often in combination with licit substances (ethanol, OTC medicines) or illicit substances, is the problem. Further, in this study of deaths involving oxycodone, the specific pain medicine OxyContin[®] (oxycodone hydrochloride controlled-release) Tablets was the only drug found in 12 (1.3% of 1014 drug abuse deaths) of the cases. Oxycodone Involvement in Drug Abuse Deaths: A DAWN-Based Classification Scheme Applied to an Oxycodone Postmortem Database Containing Over 1000 Cases, Journal of Analytical Toxicology, ISSN 0146-4760, Volume 27, Number 2, March 2003, pp. 57-67.

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would only be a problem at the borders more so than in the pharmacies. It would be a problem still on the Internet.

If we were some way able to stop OxyContin from ever coming into this country, then we would again be back to dealing with Dilaudid, Percocet, Percodan and things like that. And I want to first see if you agree with that statement. Do you believe what I just said would be correct? Yes, sir.

Mr. Raffanello. If we outvote [sic: outlaw] it, I believe it would come from outside the country or through the Internet from other countries, absolutely, someone would fill the void with all of the above. If you could not get it internally, than you see other drugs you could get, abused to a higher level to make up the difference.

Dr. Norwood. As it use[d] to be prior to OxyContin.

Mr. Raffanello. This is not a new phenomenon, people have been abusing prescription drugs since we instituted prescription drugs. It is just that now there is a lot more information out there on it.

Dr. Norwood. And my concern is that we be very, very careful and not take away this, particularly I guess for cancer patients in the country. And if you outlaw it totally then the patients who actually need it and are using it correctly no longer have it available; only those who are abusing it will have it available. So all I am saying, Mr. Chairman, is we have to be very careful how we handle this problem.³⁶

Misguided attempts – no matter how well-intentioned – to solve substance abuse problems or prescription drug abuse problems that, as a consequence, would have an adverse impact on the medical care received by the victims of accident and disease constitute an unnecessary risk imposed on an innocent population of sufferers. To date, more than 7,500,000 patients have been prescribed OxyContin by health care professionals. In the few months since launch, thousands of patients have been prescribed Palladone. The interests of these patients should not be compromised unfairly by a misguided attempt to solve substance abuse problems in this country by restricting or banning access to OxyContin, Palladone or any other FDA-approved prescription medication.

Prescription medications are vital to the public health. This includes medicines that have the potential to be abused. Issues touching on prescription medications, therefore, should be based on a full understanding of the benefits and risks associated with the use of each individual

³⁶ Hearing, Subcommittee on Criminal Justice, Drug Policy and Human Resources, Committee on Government Reform, House of Representatives, 108th Congress, Second Session, February 9, 2004.

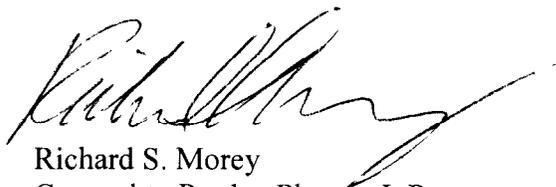
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drug. Decisions on these issues should be based on facts and data and made with a careful regard for the well being of the innocent victims of accident and disease for whom prescription medications provide relief.

Under these standards, the requests in this Petition must be denied.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Richard S. Morey', written in a cursive style.

Richard S. Morey
Counsel to Purdue Pharma L.P.

cc: Mr. and Mrs. Van Rooyan