

Charlotte Williams
FDA Dockets Management Branch
Re: Citizen Petition 2005P-0076
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June 21, 2005

Dear Ms. Williams:

The following is a second part of the response to Purdue Pharma's comments regarding the FDA Citizens' Petition to restrict the indications for the use of OxyContin and Palladone.

This petition deserves immediate attention especially since so many lives have been and will continue to be lost. If any FDA physician wishes to discuss my response, any issues, or the situation in general with me personally, I can be reached through the following numbers:
Fax: 843-293-2413; Office phone: 843-293-1022;
E-mail: sgelfand@sc.rr.com Thank you kindly.

Sincerely,



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Intracoastal Arthritis & Rheumatology
Myrtle Beach, SC

Addendum: The Response to Purdue's counsel sent by the Van Rooyans On 6/20 [dated 6/16/05, p. 8] should have noted my specialty to be Rheumatology, not Addiction Medicine.

2005P-0076

Sup 2

Response to Comments on FDA Citizens' Petition General Considerations

The motivations of counsel representing Purdue Pharma, a major drug company defending the excessive overuse of its main product, must be placed in the proper context. It is extremely disturbing that the product, OxyContin, a potentially lethal drug in the high concentrations contained in the controlled-released tablets, has become so readily available as to flood into our streets and schools, placing not only patients, but our children, at high risk of addiction or death which has repeatedly occurred. It is becoming abundantly clear that the principles of opioid pain management in cancer may not be applicable to other types of chronic pain disorders for which opioids have been freely encouraged, especially after OxyContin was approved and widely used for moderate to severe chronic pain [1]. This has resulted in a mounting volume of adverse effects, while at the same time, recent clinical studies are indicating poor long-term efficacy with a lack of favorable safety data. On the other hand, counsel representing Purdue continues to make unsubstantiated claims about the effectiveness and safety of OxyContin for patients with chronic non-cancer pain under the cover of the common problem of under-treated pain. Because of these contradictions, we now demand that peer-reviewed scientific data supporting these claims be presented by the company to the F.D.A., medical community, and public, or that the lack of this data be addressed and acted upon promptly by the F.D.A. and Congress in the context of the F.D.A. Citizens' Petition.

The broad indications for the use of OxyContin [and now Palladone], as promoted by both Purdue and a number of leading professionals in pain management [with F.D.A. approval], have been formulated in the absence of patient selectivity and safety criteria. This has significantly increased the volume of prescriptions to many chronic pain patients in whom these drugs are inappropriate, particularly those with a wide range of psychological disorders including actual drug addicts. Many of these individuals have either chronic non-malignant pain of psychogenic [central] origin, narcotic or other drug addictions, and/or secondary gain motivations. The decision to prescribe opioids in this large cohort has increased the availability and fueled the explosion of unnecessary prescriptions, dosage escalations, and the diversion of the drug through illegal sales on the street and over the Internet. A recent study of urine samples of a large group of 11,000 pain clinic patients prescribed OxyContin, found 40% of the drug was recycled among other pain clinic patients, 15% had no drug in the urine, and 15% of the total prescriptions were diverted to the black market. [2]. This type of behavior is uncommon in cancer patients who may truly benefit from this drug. Another study found that common psychiatric disorders, especially depression,

were present in 45% of opioid users, and patients with known depression, dysthymia, or problem drug use were 4 times more likely to receive opioids [3].

In the "rush to opioids" for all types of chronic pain, the role of pain-generating psychiatric co-morbidities which predispose to opioid abuse, addiction, and overdose, have often been ignored. Opioids have repeatedly become poor and dangerous substitutes for appropriate mental health care and exercise programs [e.g. rehabilitation techniques through "Mind and Muscle Management"]. These drugs are prescribed all too frequently to treat chronic pain in patients erroneously misdiagnosed or over-diagnosed with physical labels such as "arthritis" or "degenerating discs". However, good diagnostic skills and progressive management in rheumatology, behavioral science, and addiction medicine have shown that many patients with chronic non-cancer pain benefit from a rehabilitation approach which includes comprehensive exercise programs combined with learning/behavioral strategies to self-regulate anxiety and mood, while reducing and controlling non-productive cognitive processes [4]. This can help break the mindset of using high risk external substances such as opioids to attenuate intolerable subjective states including pain. These valuable self-management therapies are the best buffers for reducing drug-dependent polypharmacy so readily available at the numerous "pill-mills" and drug dealerships which have spread like wildflowers throughout the nation over the last decade.

Recent studies of primary care patients with chronic non-cancer pain have all shown a high percentage of mental disorders and substance abuse/misuse problems. Examples of these relationships include a 79% incidence of depression and a 32% incidence of drug misuse in a chronic non-cancer pain population treated at the University of North Carolina, Chapel Hill [5]. Another study of a similar cohort from the VA Connecticut Healthcare System identified a lifetime prevalence of depression ranging from 44-54%, anxiety disorders of 20-21%, alcohol abuse/dependence of 31-46%, narcotic abuse/dependence of 18-38%, and opioid abusive behaviors between 24-31% [6]. Chronic pain and substance abuse are also common features of the Post-Traumatic Stress Disorder [PTSD] [7]. Thus, the frequent co-morbidity of psychiatric and chronic pain disorders underscores the importance of diagnosing and treating underlying affective and mood disorders in each patient. This important relationship raises serious questions about both the short and long-term use and safety of opioid therapy in this patient population, a situation leading to multiple pitfalls which clearly demands further study.

It therefore is sobering that the previous premature, optimistic statements of Purdue, its representatives, and a number of pain management experts attesting to the

effectiveness and safety of long-term OxyContin and other opioids for chronic non-cancer pain provides a false sense of security which has never been substantiated by past or present published data. Furthermore, the actual adverse events of certain drugs may only become apparent after long-term studies, as recently shown by a key trial involving another painkiller, the COX-2 inhibitor, Vioxx. In a major prospective study, adverse cardiovascular events related to Vioxx did not appear until after patients were on the drug for at least 3 years [8]. Studies of opioid use in rheumatic diseases [9] and in patients attending an orthopedic spine clinic [10] were not carried out much beyond 3 months. One of the longest periods of observation in an OxyContin trial for the chronic pain of osteoarthritis was optionally extended out to 18 months. In this study, only 58 of 106 patients completed 6 months of treatment, which further decreased to 41 at 12 months, and 15 at 18 months [11]. In a recent presentation to the American Academy of Pain Medicine, Dennis Turk, Ph.D. noted that opioids reduce severe, chronic pain by only about a third, and up to 50% of patients discontinue opioid therapy because of a lack of efficacy or because of side effects. He goes on to describe the benefit of effective non-drug, cognitive-behavioral therapies [CBT] for chronic pain [12]. These studies and observations seriously question the effectiveness and safety of the long-term use of opioids for chronic non-malignant pain, even though these drugs [and particularly OxyContin] have been aggressively promoted and sold as safe and effective by Purdue and many other opioid proponents of the "pain revolution" as the major answer to the under-treatment of pain.

Many important questions remain about the value and risks of long-term opioid therapy for all types of chronic non-cancer pain. There is a limited subset of patients with chronic pain from persistent tissue disease or damage, who, after careful selectivity and screening, may benefit from chronic opioid therapy. However, these drugs are inappropriate for the majority of the chronic non-cancer pain population in whom other types of treatments [such as those mentioned above] are indicated. The problem with opioids stems from their widespread, non-selective use in the general chronic pain population [as promoted by Purdue and others], and the resultant excessive availability and ease of access of prescription opioid pills which have addicted or killed many unsuspecting victims.

A recent review article notes that "the use of opioids to treat patients with chronic non-cancer pain is controversial because of concerns about efficacy and safety, and the possibility of addiction or abuse. The results of clinical surveys and retrospective case series involving patients with non-cancer chronic pain have been inconsistent in regard to resolving these controversial issues.----- Tolerance to the analgesic and adverse effects as well as physical dependence, which causes withdrawal symptoms

upon discontinuance, may occur with opioid use. Estimates of addiction rates among patients with chronic non-cancer pain range from 3.2 to 18.9%. -----Further controlled clinical trials are needed to define the role of opioid therapy in chronic non-cancer pain, and to establish criteria for patient selection and specific treatment algorithms." [13]. Considering the definite absence of long-term safety data, the large volume of mental health problems in the chronic pain population [in both community and academic settings], and the documented sobering published statistics about abuse, addiction, overdoses, ER visits, deaths [including suicides], diversion, and crime [all from a variety of reliable sources including government-sponsored drug-monitoring agencies, drug rehabilitation centers, and law enforcement entities], and it becomes clear that this is a treacherous situation which can evolve from a national disaster into a national catastrophe.

The "irrational exuberance" of the opioid activists of the pain community and pharmaceutical industry has been questioned by other pain management leaders [14,15], as well as by older established specialties [16]. Calls for a serious reappraisal of chronic opioid therapy need to be heeded. As noted by one pain rehabilitation director in the American Pain Society Bulletin: "it is clearly inappropriate to prescribe opioids to treat chronic pain associated with depression and anxiety"----- Opioids can worsen depression.-----The argument that effective analgesia [using opioids] improves depression has never been proven.----- there are many studies suggesting that psychological function may worsen [with chronic opioid therapy].----- Patients' families often complain that patients on chronic opioid therapy have changed and that they are more irritable and anger easily." [14].

The conclusion of another recent review article, "Opioid Therapy for Chronic Pain", which appeared in the New England Journal of Medicine, notes the following:

"Current guidelines recommend a cautious approach to dose escalation and the discontinuation of opioids if treatment goals are not met. However, in busy practice settings, the reality of dealing with patients who have complex problems often forces physicians to compromise. As a consequence, very large doses of opioids are prescribed for patients with chronic pain that is not associated with terminal disease, often in the absence of any real improvement in the patient's pain or level of functioning. Whereas it was previously thought that unlimited dose escalation was at least safe, evidence now suggests that prolonged, high-dose opioid therapy may be neither safe or effective. It is therefore important that physicians make every effort to control indiscriminate prescribing, even when they are under pressure by patients to increase the dose of opioids." [15].

In spite of these warnings, there is a troublesome tendency of certain opioid proponents to use the media for sensationalizing selected case testimonials without revealing the entire clinical picture. Dr. Russell Portenoy, Head of Pain Management of Beth Israel Hospital in New York City, a leading cancer pain researcher and consultant to Purdue, recently told ABC News' Nightline about his case of a 70 year-old woman with failed spinal surgeries who could function only on exceedingly large doses of opioids: e.g. "daily doses of morphine and methadone, 20-40 times higher than a typical trauma or surgical patient would receive". The patient is interviewed and states that "I'm dependent on it to relieve my pain. I'm not addicted to it. I could stop taking it tomorrow. I'd hurt a heck of a lot, but I could stop". These types of statements leave experienced clinicians doubtful about their veracity and suspicious of addictive and illness behavior. What is not revealed are the details, e.g. the pathology [if any] of the original tissue damage, the location and type of the chronic pain, the patient's psychosocial profile, other therapies [both drug and non-drug], and prior therapeutic successes and failures. It is accepted by both parties interviewed that this patient requires inordinately high doses of opioids to function. But at what price? What are her actual mental and physical capabilities, and what are the long-term safety risks, especially considering the known profound effects of opioids on the brain? Is this patient an actual prescription drug addict who would exhibit typical addictive behavior if opioid dosages were reduced or access limited? These are the essential questions that every healthcare professional needs to ask about each patient with chronic non-cancer pain prior to considering opioid therapy.

The issue of dose escalation and opioid tolerance has recently been addressed by studies from the University of Arizona School of Medicine. The recognized phenomenon of INCREASED pain associated with long-term opioid therapy [opioid tolerance] has been traced to neuroplastic changes in the brain and spinal cord with activation of a descending CNS pathway that actually facilitates pain; higher doses may also enhance this mechanism. The authors of the study state that "these adaptive changes in response to sustained exposure to opioids indicate the need for the evaluation of the clinical consequences of long-term opioid administration." [17].

Regardless of the many rationalizations of Purdue and others, the mounting toll of adverse effects from OxyContin and other opioids has significantly increased the risk:benefit ratio of these drugs. The presence of multiple drugs in addition to oxycodone [the active drug in OxyContin] found in autopsy reports does not exclude the role of OxyContin in causing these deaths. It only indicates the extreme danger and additive effects of combining OxyContin with other psychoactive drugs and/or alcohol in a susceptible group of chronic pain patients, many of whom also have serious mental health problems which raise the risks of drug dependency, abuse,

addiction, and overdose. According to official statistics of the Florida Medical Examiners, of 333 total drug-related deaths with oxycodone during the first six months of 2004, 294 occurred in combination with other drugs [88%] while oxycodone was considered the immediate cause of death in 168 [50%]. Of these, 121 [72%] occurred in people older than 35, with 46 [27%] occurring in those over 50 years of age. 61% of the total oxycodone deaths occurred by accident. [18]. The above age groups suggest that many of these fatalities occurred in patients taking prescription oxycodone, in particular OxyContin.

It is interesting that Dr. Portenoy has now re-assessed his original enthusiasm of opioid therapy for chronic non-malignant pain. He stated on a radio talk show on the subject of chronic pain that the previous lack of concern about abuse, addiction, and diversion of opioids was a "big error" and that "doctors need to have skills in addiction medicine to use these drugs safely and effectively or they shouldn't use them at all" [19]. In an earlier interview with the San Diego Union-Tribune, he acknowledged that his original assumption that opioids posed a relatively low risk of abuse and diversion was wrong, and that "we have this terrible thing happening with OxyContin and hydrocodone, and the tragic deaths of people and terrible outcomes." [20]. Unfortunately, these consequences have occurred across a broad range of victims including many who obtained opioids through "legitimate" prescriptions, and is not confined to only those who abused these drugs such as established addicts and recreational users.

There is good reason to believe that disasters similar to OxyContin will also occur with the recently approved powerful, time-released opioid, Palladone. As summarized in a March, 2005 Medical Letter release:

"Palladone is a new long-acting formulation of the opioid agonist hydromorphone that is taken once daily for treatment of chronic pain in opioid-tolerant patients. There is no evidence that it is more effective or has fewer adverse effects than other opioids. If Palladone capsules are broken, dissolved, crushed or taken with alcohol, the entire 24-hour dose can be released at once and could be lethal, especially in non-opioid tolerant individuals." [21].

Why have we as a nation allowed this situation to fester and worsen while corporate money and politics continue to stifle debate about this growing national crisis that has claimed many more American lives than the Iraq War? Until future studies provide definitive answers to the many safety issues, risks, and efficacy of both short and long-term opioid use for chronic non-cancer pain, extreme caution and rigid patient selectivity is indicated, especially in view of the documented mounting

volume of adverse and fatal events. The "arguments" justifying the continued liberal use of OxyContin, Palladone, and other opioids in Purdue Pharma's response to the FDA Citizens' Petition [through counsel] fly in the face of these warnings, tragedies, and sad truths.



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6/20/05

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