DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Re: Docket No. FDA-2004-P-0294

Dear Mr. Attorney General:

This letter responds to your citizen petition (Petition) received on January 27, 2004.[1] The Petition requests that FDA require Purdue Pharma L.P. (Purdue) to revise the labeling of OxyContin (oxycodone hydrochloride (HCl)), controlled-release tablets, to include additional information and warnings, including an addition to the existing black box warning, about the risks of taking the drug at more frequent intervals than recommended in the current labeling for OxyContin. The Petition also requests that Purdue and FDA warn prescribers of these risks by issuing a Dear Healthcare Professional Letter and using other communication tools (e.g., safety alert, public health advisory, talk paper). We have carefully considered the Petition and comments filed in the docket.[2] For the reasons stated in this response, the Petition is denied.

I. BACKGROUND

A. OxyContin

Purdue is the holder of the new drug application (NDA) for OxyContin (oxycodone HCl) (NDA 20-553) controlled-release tablets available in 10-, 20-, 40-, and 80-milligram (mg) strengths. 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, but the only strengths currently marketed are 10, 20, 40, and 80 mg. Several abbreviated new

[1] The Petition was originally assigned docket number 2004P-0043/CP1. The number was changed to FDA-2004-P-0294 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

[2] As you state in your cover letter, the Petition is a version of an earlier document from which certain confidential information has been redacted. In preparing this response, FDA relied on the redacted version of the Petition and did not rely on any unredacted information even though it appears that you may have submitted one or more copies of an unredacted version to FDA.

We have also received a citizen petition from a different petitioner requesting that FDA (1) temporarily recall approval of OxyContin, Palladone, and generic equivalents and remove those drugs from the market until the sponsors reformulate them to be of minimal abuse potential and (2) revise the indications listed in the drugs products' labeling (this citizen petition was originally assigned docket number 2005P-0076/CP1, and its new docket number is FDA-2005-P-0325). This response does not address that citizen petition.

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drug applications (ANDAs) for oxycodone HCl controlled-release tablets have been approved by the Agency,[3] but those products are not currently marketed.[4]

OxyContin 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 "the controlled-release nature of the formulation allows OxyContin to be effectively administered every 12 hours."[5]

B. Boxed Warning

A boxed warning is the most serious warning placed in the labeling of a prescription medication. As stated in 21 CFR 201.57(c)(1), "[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. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data." The labeling for OxyContin currently has a boxed warning which states, among other things, that OxyContin can be abused in a manner similar to other opioid agonists, legal or illicit; that OxyContin is not intended for use as an analgesic that is taken as needed (prn); that OxyContin 80- and 160-mg tablets are for use in opioid tolerant patients only; and taking broken, chewed, or crushed OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

II. DISCUSSION

In the Petition, you assert that (1) the incidence of prescribing OxyContin at dosing intervals more frequent than the recommended every 12 hours (q12h) has risen at least in part because of a fundamental misunderstanding by healthcare providers of OxyContin's unique drug delivery system, (2) certain patients receiving OxyContin at intervals more frequent than q12h are more at risk of developing side effects and potentially serious adverse reactions because of the pharmacologic action of the drug, and (3) the increase in the number of doses beyond the recommended two per day increases the potential for diversion of the drug for illicit use and abuse (Petition at 2). You therefore request that FDA require Purdue to (1) strengthen the black box warning statement, (2) supplement the information and warnings in the labeling, and (3) issue a Dear Healthcare Professional letter. In the alternative, you request that FDA disseminate

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[3] *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).

[4] In the Petition, you request that the same prescribing information and warnings be required of the generic drug manufacturers if generic versions of the drug become available for sale (Petition at 55, n.75). The labeling for generic drug products is required to be the same as the labeling for the reference listed drug with certain permissible differences. See 21 U.S.C. 355(j)(2)(A)(v), 21 CFR 314.94(a)(8)(iv); see also 21 CFR 314.127(a)(7)). Therefore, if any additional warnings were added to the labeling for OxyContin, the same warnings (with permissible differences, if applicable) would also be required to be added to the labeling for generic drug products. However, because we are denying your request for additional warnings for OxyContin, your request that the same prescribing information and warnings be required for generic drug products is also denied.

[5] Dosage and Administration section of the labeling. See also, e.g., Pharmacokinetics and Metabolism section of the labeling ("OxyContin Tablets are designed to provide controlled delivery of oxycodone over 12 hours"), Individualization of Dosage section of the labeling ("It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h").

these warnings through a Safety Alert, Public Health Advisory, Talk Paper, or Urgent Notice (Petition at 9-11).

For the reasons described below, we believe that the information you have provided regarding prescribing data and safety information does not support your conclusion that patients receiving OxyContin at intervals more frequent than q12h are more at risk of developing side effects and potentially serious adverse reactions. You also have not provided sufficient evidence to demonstrate that dosing OxyContin more frequently than q12h may also increase the potential for diversion or abuse. We therefore deny your request for a black box warning statement, additional warnings and information in the labeling, and the issuance of a Dear Healthcare Professional letter, Safety Alert, Public Health Advisory, Talk Paper, or Urgent Notice. Although we are denying your request, we recognize that the possible misuse or abuse of OxyContin raises serious safety concerns, and we will continue to closely monitor the safety of OxyContin and take actions as we believe appropriate.

A. The Petition Fails to Provide Sufficient Evidence that Prescribing OxyContin for Dosing More Frequently than q12h is Associated With an Increased Risk of Adverse Reactions

You assert that Purdue purchases data products from IMS Health for information regarding prescription practices (Petition at 14). You also assert that relevant data show that prescribers are prescribing OxyContin "off-label" by prescribing OxyContin at dosing intervals more frequent than q12h (Petition at 16). You state, "This trend of prescribing outside the recommended dosing schedule continued to [redacted] moving to [redacted] in 2000 [redacted] in 2001, before dropping slightly to [redacted] in 2002 (Petition at 16).[6] You also assert that in a study reported in the *Journal of Managed Care Pharmacy* in 2003, researchers studied prescribing trends and of the 437 OxyContin patients studied from six states (including Connecticut), the mean frequency of administrations per day was q8h, and the average time interval between administrations was 7.8 hours. Only 17.5% of the OxyContin patients surveyed had an average interval between administrations of 12 or more hours (Petition at 16). You state that the study concluded that OxyContin appears to be used in a manner inconsistent with the labeling (Petition at 16).

You assert that the incidence of such prescribing has risen at least in part because of a fundamental misunderstanding by healthcare providers of OxyContin's unique drug delivery system. You assert that such a practice may adversely affect the health of certain patients who are prescribed the drug in this manner, and you state that prescribers are apparently unaware that in doing so, they may be placing their patients at risk of incurring increased incidence of side effects and possibly serious adverse reactions due to the pharmacologic action of OxyContin when prescribed in this manner (Petition at 8).

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[6] It is not clear how you determined that the number of OxyContin prescriptions written for dosing q8h or more frequently has increased over time. We note that if you made this determination without "denominator" data that include the total number of prescriptions dispensed, it would not be possible to evaluate whether greater numbers of higher frequency dosing reflect (1) an increase in numbers of cases due to larger numbers of prescriptions dispensed or (2) an increase in the proportion of prescriptions with higher frequency dosing.

Although physicians may be prescribing OxyContin for dosing more frequently than q12h or "off-label" in the course of their practice of medicine, we disagree with your fundamental premise that prescribing OxyContin for dosing more frequently than q12h is associated with an increased risk to patients of side effects and possibly serious adverse reactions because, among other factors, it fails to take into account the need to increase the total daily dose in the patient who complains of pain on any given total daily dose and dosing regimen of OxyContin. Below we provide background regarding "off-label" use, the practice of medicine, and the need for individualized treatment in the use of opioids. Then, in section II.A.2 of this response, we discuss our analysis, concluding that the Petition fails to provide sufficient evidence to demonstrate an association between more frequent dosing and adverse events.

1. Prescribing OxyContin at Dosing Intervals More Frequent than q12h and the Practice of Medicine

Pain is challenging to treat with opioids because of interpatient pharmacodynamic variability and variability in levels of tolerance. Although opioids obey typical pharmacologic principles of increasing efficacy and increasing adverse events with increasing dose, there is substantial interpatient pharmacodynamic variability.[7] Because of this interpatient variability, it is important that physicians individualize the treatment and dosing for each patient.[8] The proper clinical management of chronic pain patients necessitates the use of potent opioids such as OxyContin at doses and dose regimens that provide the best ratio of efficacy to safety.

In addition, opioids induce tolerance, and from a pharmacokinetic perspective, opioids are unusual in the pharmacologic armamemtarium in that they have no maximum dose. Because opioids have no dose ceiling (some chronic pain patients require total oxycodone doses well exceeding 1000 mg, the highest dose described in the labeling), a physician could determine, in his or her medical judgment, that dosing any particular strength at intervals shorter than q12h is part of rational therapy for certain patients and would result in an efficacy benefit with a tolerable adverse event profile.

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[7] Clinical pharmacology studies conducted to support NDAs typically enroll healthy volunteers who are on no concomitant medications. The purpose of the study is to understand the absorption, metabolism, and elimination of the drug in "normal" people. However, as complex organisms, humans do not always absorb and eliminate drug products identically. Even within a well-controlled clinical pharmacology study where healthy subjects are dosed identically, there could be considerable intersubject variability in the results. The variability in actual patient populations may be even greater. For example, the actual patient population for OxyContin may range from relatively healthy young people to geriatric patients with multiple medical problems on multiple medications that could affect the absorption, metabolism, or excretion of the drug.

[8] The labeling for OxyContin also recognizes the importance of individualized opioid dosing. The Dosage and Administration section of the labeling states, "In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment." The Indications and Usage section of the labeling also states, "Physicians 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 Healthcare Research and Quality (formerly known as the Agency for Healthcare Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society".

To account for patient differences, physicians could be prescribing potent opioids such as OxyContin off-label. As you recognize in the Petition,[9] off-label use of a drug product occurs when a physician, in his or her practice of medicine, prescribes an approved drug product for a use or in a manner that is not consistent with the FDA-approved labeling of the drug product. FDA does not restrict such usage when the use is within the practice of medicine, although FDA does prohibit the promotion of a drug product for an off-label use.

The labeling for OxyContin recommends q12h dosing because the clinical trials used to support approval used that dosing paradigm,[10] and the pharmacokinetic data used to support approval of the NDA were consistent with a 12-hour dosing interval.[11] While a 12-hour dosing interval would be expected to be optimal for most patients, it is possible that some patients will require a more or less frequent dosing schedule to account for individual pharmacokinetic and pharmacodynamic differences. Therefore, despite the information in the labeling pointing towards q12h dosing, it may be the case that in their practice of medicine, physicians are prescribing OxyContin off-label at dosing intervals more frequent than q12h to account for patient differences.

We also note that for pharmacokinetic and pharmacodynamic reasons, a substantial proportion of chronic pain patients will experience inadequate analgesia toward the end of the dosing interval, known as "end-of-dose failure."[12] From a pharmacokinetic perspective, the goal of opioid therapy is to maintain plasma opioid concentrations above a threshold for efficacy but below the concentration where unacceptable adverse events occur. We recognize that when faced with the complaint of end-of-dose failure, the physician may consider a number of options, including the following:

- Decrease the dosing interval and either keep the total daily dose constant or increase the total daily dose
- Add a short-acting analgesic to be used toward the end of the dosing interval
- Increase the dose, maintaining the previous dosing interval

Selection by the physician of one of these options in his or her clinical judgment in the practice of medicine may account for some of the prescribing practices you cite. The choice to increase the dosing frequency, can at times, be safer than increasing the total daily dose at the q12h dosing interval, as it may be possible to achieve adequate pain control throughout the 24-hour

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[9] In the Petition, you acknowledge that prescribing a drug in a manner that is inconsistent with the manufacturer's labeling is considered "off label" prescribing, and although FDA regulations prohibit a manufacturer from marketing its drug for off-label uses, prescribers are not so constrained (Petition at 17). You state that physicians commonly prescribe drugs for uses not indicated in the drug's package insert, and concern arises if off-label use presents a safety risk to the patient (Petition at 17).

[10] The Individualization of Dosage section of the labeling states, "It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h."

[11] See the Pharmacokinetics and Metabolism section of the labeling.

[12] As discussed in section II.A.2.a of this response, the Petitioner provides the opinion of Dr. Alexandros Makriyannis, a medicinal chemist, who also recognizes the issue of end-of-dose failure (Petition at 25).

period with a lower total daily dose, and a lower maximum drug concentration, by using q8h dosing.

2. The Petition Fails to Provide Sufficient Evidence to Demonstrate an Association Between More Frequent Dosing and Adverse Events

In the Petition, you assert that patients receiving OxyContin at intervals more frequent than q12h are more at risk of developing side effects and potentially serious adverse reactions (Petition at 2). In support of your assertions, you provide the opinion of a medicinal chemist, the opinion of a toxicologist, MedWatch information, and patient and family member interviews. For the reasons described in greater detail below, you have failed to provide sufficient information to demonstrate an association between dosing OxyContin more frequently than q12h and an increased risk of developing side effects and potentially serious adverse reactions.

a. Drug concentrations in plasma

You assert that the practice of prescribing OxyContin at intervals shorter than q12h could increase oxycodone blood levels above the level deemed safe through clinical testing when the extra dose is accompanied by an increase in the patient's total daily oxycodone dose, and the higher drug concentrations in plasma may increase the risks of side effects in patients taking OxyContin (Petition at 20, 21-22). You provide the opinions of Dr. Alexandros Makriyannis, a medicinal chemist, and Dr. James O'Brien, a toxicologist, in support of your assertions.

Dr. Makriyannis asserts that taking the same individual doses of OxyContin q8h instead of q12h would result in a significant increase in the oxycodone concentration at hours 9 and 10 of the first dose because of the additive effect of the two doses (Petition at 24). Dr. Makriyannis believes that prolonged prescribing in this manner could lead to increased steady-state levels of the drug with the risk of undesirable side effects (Petition at 24). You state that Dr. Makriyannis believes that physicians may be prescribing OxyContin outside the manufacturer's recommended guidelines to compensate for end-of-dose failure (Petition at 25). While he does not see much risk at the lower OxyContin strengths, he believes that increasing the total daily dose by prescribing the drug at intervals shorter than q8h, especially for the higher OxyContin strengths, may lead to high concentrations of oxycodone with potentially undesirable side effects (Petition at 25).

Dr. O'Brien also asserts that prescribing OxyContin q8h will cause a build-up in the plasma concentration of oxycodone in the patient before steady-state is reached (Petition at 27). Dr. O'Brien asserts that prescribing OxyContin q8h or more frequently will significantly raise the potential for a patient to incur an increase in the frequency and severity of side effects and possibly adverse events, particularly within the first few days after dosage adjustment, and this concern is intensified for those patients whose ability to eliminate the drug is compromised due to age, gender, or disease (Petition at 25-27).

We agree that if patients are prescribed the same dose at more frequent intervals (resulting in a higher total daily dose), they would be expected to experience higher drug concentrations in plasma. However, we believe that the risks and benefits to patients are more complicated and

require consideration of additional factors. As explained in section II.A.1 of this response, there is tremendous intersubject variability in pain patients. Therefore, q12h dosing may result in end-of-dose failure for some patients. In changing the dosing frequency from q12h to q8h, we expect that physicians may adjust the milligrams per dose to keep the total daily oxycodone dose consistent, which would have the effect of maintaining a more even plasma oxycodone concentration. If dosing q8h resulted in inadequate analgesia, we expect that a physician would most likely increase each dose, resulting in a higher total daily dose and higher average plasma concentrations.

Higher plasma concentrations may result in more adverse events. For the majority of individual patients, there is a reasonably consistent dose relationship between efficacy and adverse events; increasing the plasma opioid concentration will affect more analgesia and may increase the rate and/or severity of adverse events. As discussed, a substantial proportion of patients experiencing end-of-dose failure require a change in dose or dosing interval. Therefore, when done as part of individualized therapy, a physician's decision to increase the total daily dose, via a change to q8h dosing or with continued q12h dosing, would be expected to improve benefits while potentially increasing adverse events. It is then the responsibility of the physician to inform the patient and caregivers to monitor for the impact of that dosing change on the adverse event profile and report any increases that are problematic. A data analysis of the Adverse Event Reporting System (AERS) data failed to show a correlation between adverse events and increased dosing frequency, as explained in section II.A.2.b of this response.

Although we agree with Dr. Makriyannis' prediction that plasma oxycodone concentrations would increase (assuming that the total daily dose is increased by 50% because the dosing frequency is changed from q12h to q8h), we believe that whether or not the higher steady-state oxycodone plasma concentrations will lead to more adverse events depends on each individual patient. There is substantial variability in the pharmacodynamic effects and concentration-time curves between patients, and Dr. Makriyannis did not address the wide variability in the pharmacokinetics and pharmacodynamics for opioids in the patient population. Also, higher steady-state concentrations from more frequent dosing (assuming that the strength was kept constant, resulting in a higher total daily dose) could be appropriate for an individual patient and result in improved efficacy with no worrisome increase in side effects.

Again, assuming an increase in the total daily dose, we agree with Dr. O'Brien's statement that prescribing OxyContin q8h or more frequently would increase oxycodone plasma concentrations. If the decision to increase the dose were to result in excessive blood levels, it is reasonable to expect those effects to become evident in the first few days after the regimen is changed. However, Dr. O'Brien's analysis is limited to the predicted effects of higher frequency dosing on plasma oxycodone concentrations and the general dose-relationship between adverse events and plasma oxycodone concentration. Opioids, including oxycodone, have no dose ceiling based on a plateau for efficacy. Additionally, as patients develop tolerance, they are better able to tolerate the side effects of opioids. Therefore, there is no maximum dose for opioids. What is important is to titrate the dose of an opioid carefully so that there is an opportunity to monitor for safety and toxicity. To limit the assessment of a change in dosing regimen to the potential effect on safety fails to account for the benefits from the dosing regimen, which should also be considered. The proper clinical management of chronic pain patients

necessitates the use of potent opioids such as OxyContin at doses and dose regimens that provide the best ratio of efficacy to safety.

b. MedWatch and AERS data

You state that you reviewed and analyzed MedWatch reports for OxyContin or oxycodone hydrochloride (controlled-release) submitted to FDA by Purdue and/or health professionals covering the time period from 1999 through early 2003 (Petition at 34). You state that you attempted to quantify the number of adverse event reports submitted for patients with a prescription for OxyContin q8h or more frequently (despite limitations of the reports, including the difficulty of determining whether a report was submitted to FDA more than once because the identification of the patient and the health professional were redacted by Purdue) (Petition at 34-35). You state that you tried to compare this information with the information contained in Purdue's documents pertaining to the percentage of OxyContin prescriptions written q8h or more frequently to determine whether it was more likely than not that there was a correlation between a prescription written for dosing q8h and an adverse event (Petition at 35).

Of the 2,880 adverse event reports you reviewed and analyzed, you concluded that 1,106 were most likely related to a patient prescribed OxyContin (Petition at 35). Of those reports, you identified 795 reports where the prescription, including dosing frequency, was mentioned in the report (Petition at 35). Of those cases, you state that patients were prescribed OxyContin q8h or more frequently in 247 or 31% of the adverse events reported (Petition at 35).

You conclude that your statistical findings indicate there is a much greater percentage of OxyContin adverse events reported to MedWatch with a prescription for q8h or more frequently than would be expected based on the overall percentage of prescriptions written in that manner (Petition at 37). You believe that given the significant percentage differential between the number of OxyContin prescriptions written for dosing q8h or more frequently, and the percentage of adverse event reports that have such prescriptions, a sufficient basis exists from which FDA may conclude that there is a correlation between increasing the dosing frequency of OxyContin prescriptions and the potential for an adverse event (Petition at 37). You also note that the Los Angeles County Department of the Coroner conducted a study of 58 deaths where oxycodone was detected during the postmortem evaluation. Of those 58 deaths involving oxycodone, 27 were determined to involve the controlled-release form of the drug. In 14 of the 27 cases, intact tablets were found in the stomach, which led the authors of the study to question whether the cause of death was suicide or some other reason such as the individual's misunderstanding of the proper administration of the painkiller (Petition at 37). The authors of the study observed that in many of the 27 cases, prescriptions were found for the administration of OxyContin 3, 4, and even 6 times a day (Petition at 38).

Based on our review of the information you have provided and our own analysis of safety data from the AERS database, we have concluded that you have failed to demonstrate that there is a correlation between prescribing OxyContin at dosing frequencies more frequent than q12h and the potential for an adverse event. Based on our own analysis, we have found that dosing OxyContin at higher frequencies than q12h is not shown to be associated with an increased proportion of adverse events.

MedWatch is the FDA Safety Information and Adverse Event Reporting Program and serves both healthcare professionals and the medical product-using public.[13] Through MedWatch, we obtain important and timely clinical information about safety issues involving medical products, including prescription and over-the-counter drugs. A component of the safety information available through MedWatch is AERS. AERS collects information about adverse events, medication errors, and product problems that occur after the administration of approved drug and therapeutic biologic products, and certain AERS data is available on the FDA's Web site.[14] Healthcare professionals, patients, and others may report adverse events either directly to FDA or to the holder of the NDA for the drug product who then is required to forward the report to FDA.[15] Because of the voluntary nature of the reporting system, not all adverse events may be reported, and reports that are submitted are often incomplete.

In addition to reviewing the information in the Petition, we have reviewed the AERS database for U.S. cases with known dosing frequency and OxyContin as a suspect drug from the time of the beginning of marketing in January 1996 to October 20, 2004.[16] Of a total number of 7,019 OxyContin AERS reports, 1,349 reports had known dosing frequency, and of those reports, the dosing frequency was as follows:

1,040 (77%) were twice daily (BID)
237 (18%) were three times a day (TID)
59 (4%) were four times a day (QID)
13 (1%) were greater than four times a day

In general, the OxyContin reports in AERS represent a fraction of the actual number of adverse events that have occurred as a result of OxyContin exposure in the population. Of the 1,349 reports with known dosing frequency, almost all (1,304 or 97%) of the outcomes were serious. In addition, there were 414 deaths reported, which represented 31% of the 1,349 AERS reports where dosing frequency was known.

Based on our analysis of the AERS data, higher dosing frequency did not appear to be associated with fatal outcomes, the most serious adverse event. In fact, there was a somewhat higher proportion of reports of fatalities with BID dosing than with the other dosing groups. This does not mean that there was necessarily a higher risk of fatalities associated with BID dosing, as

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[13] Information about MedWatch is available at http://www.fda.gov/medwatch/index.html.

[14] MedWatch Safety Information is available at http://www.fda.gov/medwatch/safety.htm.

[15] See 21 CFR 314.80.

[16] You state that you reviewed MedWatch reports from 1999 to early 2003 provided to you by Purdue. We have also conducted our own analysis of AERS data for the time period from the beginning of marketing for OxyContin in 1996 to 2004, which we believe is an appropriate and representative time frame for the purposes of independently analyzing the claims in the Petition. We are not aware of any additional safety signals in recent years that would materially change the results of our analysis. Given that your claims in the Petition are based on an analysis of reports from 1999 to 2003, an FDA analysis that includes recent years may not be appropriate for the purposes of evaluating the claims made in the Petition. Independent of our analysis and response to the Petition, however, we continue to monitor OxyContin for safety issues.

there were unidentified variables that contributed to the fatalities, which were not contained in the AERS dataset.

In the Petition, you assert that Dr. Makriyannis believes that increasing the patient's total daily dose of oxycodone by prescribing the drug at intervals shorter than q8h, especially for the higher OxyContin strengths, may lead to high concentrations of oxycodone with potentially undesirable side effects (Petition at 25). We also analyzed the AERS reports to examine whether a prescribed higher total daily dose was associated with greater numbers of deaths and whether a causal link could be found. The total daily dose prescribed was divided into three individual dosing categories: under 80 mg, 80-160 mg, and greater than 160 mg. Patients who were prescribed the highest daily dose, greater than 160 mg, had a larger proportion of fatal outcomes compared to the other dosing groups. However, because there may be other factors associated with the higher dosages as well as with higher fatality rates (e.g., intractable cancer pain, completed suicide), it is not appropriate to conclude that higher total daily dosages are causally associated with fatality. Use of higher dosage strengths also may indicate a population that is more ill or may reflect accidental or intentional overdose resulting in an adverse event. In the AERS reports, while there was a larger proportion of higher dosage forms found with less than q12h dosing, and a larger proportion of fatalities with higher dosage forms noted, it still is not appropriate to attribute these fatalities to this type of OxyContin use.

You also asserted that the potential increase in side effects from high frequency dosing in the elderly is more pronounced because of a slight reduction in their ability to eliminate oxycodone from their systems (Petition at 23). We examined the AERS reports to determine whether this was the case, and reports of high frequency dosing were not disproportionately composed of elderly patients. The high frequency dosing cases in the elderly did not appear to be associated with a higher risk of fatalities, but given the small numbers, it is not possible to confirm or refute any associations.

Finally, you assert that there is a much greater percentage of OxyContin adverse events reported to MedWatch with a prescription for q8h or more frequently than would be expected based on the overall percentage of prescriptions written in that manner based on prescribing data that you obtained from Purdue (Petition at 37). You conclude that therefore a sufficient basis exists from which FDA may conclude that there is a correlation between increasing the dose frequency of OxyContin prescriptions and the potential for an adverse event (Petition at 37).

We disagree with your assertions. Comparing the figures from MedWatch reports and from prescribing data such as from IMS Health is not a valid comparison because the two datasets use very different methodologies to obtain information. Any comparisons between prescribing data such as from IMS Health and AERS data need to be considered with caution because AERS reports are submitted to FDA spontaneously and do not represent the entire universe of all adverse events. Furthermore, the dosing information was reported in only 1,349 reports, which is 19% of the total number of 7,019. Additionally, in our analysis of AERS data, of the 588 reports that had a known date for the adverse event, the date on 329 of these reports did not match the year that the report was received by FDA, which would further complicate efforts to determine trends over time. Therefore, we disagree that a sufficient basis exists for us to

conclude that there is a correlation between increasing the dose frequency of OxyContin prescriptions and the potential for an adverse event.

For the reasons described, we conclude that the information in the Petition fails to provide sufficient evidence to demonstrate a correlation between dosing more frequently than q12h and adverse events. Our analysis of AERS data also does not support your claim that higher frequency dosing is associated with an increased proportion of adverse events. Dosing frequency was not associated with fatal outcomes, and although higher total daily dosages were associated with fatal outcomes, it cannot be concluded that the higher total daily dosages are causally associated with fatalities given that other variables have not been measured.

c. Interviews

You state that you have conducted interviews with former OxyContin patients or family members of such patients who describe serious side effects that they believed were caused by the drug, or with family members who believe that OxyContin was a precipitating factor in the patient's death (Petition at 28). In particular, you discuss an interview with John Doe and with Chelly Griffith. In relation to each of these interviews, you also discuss certain MedWatch reports. As described below, the information you have provided fails to demonstrate that more frequent dosing of OxyContin than recommended in the labeling is associated with an increased occurrence of side effects and adverse events.

i. Interview with John Doe and MedWatch information

You discuss your interview with John Doe, whose wife suffered from Lyme disease and Graves' disease and was taking several medications including OxyContin (Petition at 28). John Doe believes his wife's death was a result of her use of OxyContin (Petition at 29). John Doe's wife was initially prescribed 10 mg of OxyContin q8h which was eventually increased to 80 mg q8h (Petition at 28). Based on John Doe's statement that his wife was prescribed OxyContin and her oxycodone blood levels, the medical examiner concluded that she died as a result of an OxyContin overdose (Petition at 29).

While the death of John Doe's wife was a tragic event, this isolated incident does not provide the necessary information and data to support your conclusion that there is an association between the frequency of dosing and adverse events. There may be other factors that were associated with the death of his wife, such as the higher total daily dose of OxyContin or issues in her medical history.

The brief information available in this anecdote is consistent with our findings in our analysis of AERS data. While we found that there was no correlation between higher frequency dosing and serious adverse events, we found a correlation between total daily dosages greater than 160 mg (such as in the case of John Doe's wife), and serious adverse events. However, as we noted in section II.A.2.b of this response, because there may be other factors associated with both the higher dosages and with the higher fatality rates, it is not possible to conclude that higher total daily dosages are causally associated with fatality.

In connection with your John Doe interview, you also discuss certain MedWatch adverse event reports. You state that your review of MedWatch adverse event reports submitted to FDA from 1999 through early 2003 identified 49 adverse event reports where death was the outcome, and all of these reports indicate that the decedent was prescribed OxyContin at least q8h or more frequently (Petition at 29-30). You state that your review of these 49 reports revealed 12 deaths where OxyContin may be considered a suspect cause (Petition at 29). You provide excerpts from these MedWatch reports on pages 29-30 of the Petition.

The information from these reports is not sufficient to support the conclusion that q8h or more frequent dosing of OxyContin is associated with the patient's death because other factors may be associated with the deaths, including the increase in the patient's total daily dosage of OxyContin, issues in the patient's medical history, and use of other medications. Therefore, a causal relationship between more frequent dosing and the patients' deaths cannot be assumed. We also note that in certain cases, the patient's total daily dosage was increased to the higher range of total daily doses of above 160 mg, which is consistent with our analysis that higher daily dosages were associated with fatal outcomes.

ii. Interview with Chelly Griffith and MedWatch information

You discuss your interview with Chelly Griffith, a 37-year-old female (Petition at 30). In January 1999, Ms. Griffith aggravated a prior back injury and was given a prescription for OxyContin 20 mg q12h (Petition at 30). Within days of beginning this treatment regimen, she experienced dizziness, tiredness, and constipation, and although she continued to take the medication, she complained to her physician that the OxyContin did not effectively control her pain (Petition at 30-31). Her physician recommended increasing her total daily dose from 40 mg to 60 mg by increasing the frequency of administration of her 20 mg dose from q12h to q8h (Petition at 31). She experienced side effects including significant weight loss, dizziness, severe itching, nausea, abdominal pain, and a "floaty" or "buzz-like" feeling within the first one or two hours of taking each dose, and she developed an intense uncontrollable craving for OxyContin (Petition at 31). By summer of 2000, her physician increased her prescription to 40 mg q8h in an effort to treat her inadequate pain control (Petition at 31). She experienced intensified side effects including numbness throughout her body, double-vision, loss of smell and taste, tinnitus, decreased libido, and urine retention (Petition at 31-32). After various attempts, she ultimately weaned herself from the medication (Petition at 32).

The information you provide from this interview is insufficient to support your conclusion that there is an association between the frequency of dosing and side effects or adverse events. There may be other factors associated with the side effects, such as the higher total daily dose of OxyContin and issues in her medical history. In addition, one case is insufficient to make such a generalization.

In connection with your interview of Chelly Griffith, you also discuss certain MedWatch adverse event reports. You state that you identified 247 adverse event reports submitted to FDA from 1999 through early 2003 where the patient was prescribed OxyContin at least q8h or more frequently (Petition at 32). You state that your review of these reports revealed 52 non-fatal serious adverse events where OxyContin may be considered a suspect cause of the event and

which resulted in a life-threatening event, hospitalization, or some other medically significant outcome (Petition at 32-33). You provide excerpts from these Medwatch reports on pages 33-34 of the Petition.

The information in these reports is not sufficient to support the conclusion that q8h or more frequent dosing of OxyContin is associated with these adverse events because other factors, including the increase in the patient's total daily dosage of OxyContin, issues in the patient's medical history, and use of other medications may be associated with these adverse effects. Therefore, an association between more frequent dosing and the adverse events cannot be assumed, given the complex and individualized nature of pain treatment.

For the reasons described, the information you provide in the interviews and the MedWatch reports is insufficient to support any conclusion about the relationship between dosing more frequently than q12h and an increased risk of side effects or adverse events.

B. The Petition Fails to Provide Sufficient Evidence to Demonstrate That Increased Dosing Frequency Presents Greater Risk of Diversion and Abuse

You assert that increased dosing frequency may contribute to abuse and diversion of OxyContin (Petition at 40). We discuss these issues in greater detail below.

1. Diversion

You assert that increased dosing frequency may contribute to the abuse and diversion of OxyContin because if the pain is adequately controlled at q12h, a patient may sell the extra daily dose (Petition at 40).

While we would agree with the general proposition that if the total daily dose of OxyContin is increased, it will result in larger amounts of oxycodone in the community and larger amounts potentially available for diversion, we believe that you have failed to present sufficient evidence that prescribing OxyContin more frequently than q12h is associated with an increased risk of diversion. You failed to present any data to support your speculation that prescribing OxyContin at q8h presents a comparatively greater risk of diversion than other potential scenarios, such as prescribing OxyContin at q12h to patients who may not need the medication at all or whose pain may be adequately controlled with one tablet per day.

The diversion of OxyContin is a serious issue, and we recognize the risks of diversion of OxyContin regardless of the dosing regimen. We are continuing to evaluate the risks of abuse, misuse, and diversion and ways of addressing these issues both through our authority under the Federal Food, Drug, and Cosmetic Act and in partnership with other federal, state, and local governmental agencies.

2. Abuse

You assert that prescribing OxyContin at frequencies greater than q12h may contribute to the abuse of OxyContin (Petition at 40). In support of your claims, you provide the opinions of Dr. Makriyannis and Dr. O'Brien. Dr. Makriyannis states that addiction is often related to several factors including (i) the patient's genetic predisposition, (ii) the dosage, (iii) the time to onset of drug effects, and (iv) the frequency of administration. Dr. Makriyannis states that thus, an increase in the total daily dose of oxycodone due to the accelerated frequency of administration could increase the probability for addiction (Petition at 25). Dr. O'Brien states that because of OxyContin's biphasic delivery system, prescribing OxyContin q8h or more frequently will raise the likelihood of increased euphoria, which will add to the potential for abuse and psychological dependence on the drug (Petition at 28).

We believe that you have failed to present sufficient evidence that prescribing OxyContin more frequently than q12h may be associated with an increased risk of abuse. The statements of Dr. Makriyannis and Dr. O'Brien fail to demonstrate that an increased dosing of OxyContin would lead to an increased risk of abuse because other factors would need to be considered. With respect to Dr. Makriyannis' statement, many of the risk factors for addiction are still under debate by experts. There is consensus that there is a genetic component to addiction and that frequency of administration and a short time for the time to maximum concentration (T_{max}) increases the risk of addiction. However, those risks must be assessed in the context of each patient's individual need for analgesia. Furthermore, known pharmacokinetic principles support the conclusion that extended-release products will decrease spikes in the concentration of opioid, resulting in a smoother concentration-time curve compared to an immediate-release product. Based on pharmacokinetic principles, more frequent administration of an extended-release opioid produces smaller fluctuations in blood levels. In current thinking about rewarding behavior, a smoother pharmacokinetic profile would be expected to result in less reinforcement, which may lead to less potential for abuse. We expect these principles to apply to the administration of OxyContin.

With respect to Dr. O'Brien's statement, while his opinion regarding pharmacokinetics is within accepted pharmacokinetic principles, he does not consider biologic variability, dose individualization, and the benefits of improved pain control, which would also affect the potential for abuse.

Therefore, for the reasons described, we believe that you have not provided sufficient information to support your conclusions that prescribing OxyContin at intervals less than q12h may be associated with a greater risk of diversion and abuse.

C. The Petition Fails to Provide Sufficient Evidence to Support the Requested Labeling Changes and Warning Communications

You assert that practitioners and the public have not been fully informed of the potential risks associated with the prescribing of OxyContin at dosing intervals more frequent than q12h (Petition at 9). You therefore request that FDA (1) require Purdue to strengthen the black box warning statement, (2) supplement the information and warnings in the labeling, and (3) issue a

Dear Healthcare Professional letter (Petition at 9-11). In the alternative, you request that FDA disseminate these warnings through a Safety Alert, Public Health Advisory, Talk Paper, or Urgent Notice (Petition at 11). You also assert that the fact that medical journals mistakenly reported that the suggested or suitable dosing schedules for OxyContin were q8-12h highlight your conclusion that the current warnings in the drug's labeling are inadequate to inform prescribers and patients of the potential for side effects and adverse reactions due to dosing frequencies of OxyContin in excess of q12h (Petition at 38-39). You assert that because the labeling does not include the additional warning information you request, the labeling may be considered misbranded under the Federal Food, Drug, and Cosmetic Act (Petition at 53).

As we have explained in this response, the Petition fails to provide the quantity and quality of scientific evidence needed to support your fundamental premise that prescribing OxyContin at dosing intervals more frequent than q12h increases the potential for side effects and adverse reactions and the potential for abuse and diversion.[17] Our analysis of relevant data also does not support your premise. As described below, we disagree that the product would be misbranded without the changes you request and therefore deny your requests.

1. Boxed warning

You request that a black box warning be added to OxyContin's labeling that states, "The recommended dosing guideline for OxyContin is q12h. The side effect profiles and other clinical documentation only support this dosing schedule. Increasing the patient's total daily oxycodone dose by adding one or more doses is not within the recommended dosing guidelines. Dosing OxyContin at intervals of q8h or shorter may cause an increase in oxycodone plasma concentrations and thereby increase the risks of side effects such as euphoria and sedation. Proper dosing further minimizes the potential for abuse and diversion" (Petition at 10).

We disagree that the proposed boxed warning should be added to OxyContin's labeling. As discussed, you have not provided sufficient evidence to support the box statements that you request. You have failed to demonstrate that dosing OxyContin at intervals of q8h or shorter would "thereby increase the risks of side effects." You also have failed to demonstrate that "proper dosing further minimizes the potential for abuse and diversion." In addition, the Petition asserts that dosing more frequently than q12h may increase the risk of abuse and diversion but does not provide evidence to support the assertion that proper dosing would minimize the potential for abuse and diversion.

[17] You also assert that Purdue has information that its drug is being prescribed outside the recommended dosing guidelines (Petition at 41). You assert that Purdue has not attempted to explicitly or expressly communicate the warning to all prescribers of the potential health consequences and increased diversion inherent with more frequent dosing intervals, including those who continue their off-label prescribing practices without informing Purdue (Petition at 44). You also make certain allegations regarding Purdue's knowledge regarding prescribing practices and assert that Purdue has a responsibility to update and inform health professionals of safety issues accompanying the use of its drug (Petition at 47-53). Because we disagree with your assertions that additional warning information should be added to the labeling or disseminated through letters or Safety Alerts, your allegations regarding Purdue's actions are moot.

2. Additional warning and safety information in the labeling

You request that warning information be added to the specified sections of the labeling to state, among other things, that increasing the patients' total daily dose of oxycodone by prescribing OxyContin at intervals shorter than q12h will increase oxycodone concentration in the plasma to levels that may exceed the levels depicted in the OxyContin labeling, and that titrating the patient in this manner by increasing the dosing frequency to q8h or more frequently will cause acute successive increases in plasma concentrations of oxycodone and is not within the recommended dosing guidelines (Petition at 10). You also request that information be added to the labeling that states that increasing the daily dose of oxycodone by increasing the dosing frequency will alter the side effect and adverse reaction profiles contained in the OxyContin package insert and titrating the patient's total daily dose of oxycodone by shortening the interval between administration to less than q12h for the 80-mg and 160-mg[18] doses of OxyContin further increases the already heightened risks attendant with prescribing these dosage strengths (Petition at 10-11). You also request that this information be added to relevant sections of the labeling and that adverse drug reactions associated with this dosing schedule identified and reported during post-approval use of OxyContin should be included in a Post-Marketing Experience section added to the labeling (Petition at 11).

We disagree that the additional warning information you request should be added to the labeling. As described in this response, you have not provided adequate data to support the assertions in the requested warning statements. In addition, our analysis of safety data found no correlation between prescribing OxyContin at intervals shorter than q12h and the occurrence of adverse events.

3. Dear Healthcare Professional Letter and/or FDA Warnings

You request that we require Purdue to inform all prescribers of controlled substances about the potential risks of prescribing OxyContin at dosing intervals shorter than q12h by issuing a Dear Healthcare Professional letter (Petition at 11). You request that in addition to or as an alternative to action by Purdue, we should disseminate the warnings through a Safety Alert, Public Health Advisory, Talk Paper, or Urgent Notice (Petition at 11).

We disagree that we should require Purdue to issue a Dear Healthcare Professional letter or that we should issue our own warnings regarding this issue. For the reasons discussed in this response, you have failed to provide adequate data to support your request for additional warnings to be disseminated to prescribers and the public, and our analysis of safety data found no correlation between prescribing OxyContin at intervals shorter than q12h and the occurrence of adverse events events.

[18] As you acknowledge in the Petition and as stated previously, the 160-mg strength is no longer marketed.

4. The absence from the labeling of the additional warning information you request does not render OxyContin misbranded

You assert that OxyContin may be considered misbranded under the Federal Food, Drug, and Cosmetic Act because information contained in the drug's labeling fails to fully disclose potential risks incident to prescribing OxyContin q8h or more frequently, and inaccurately describes the incidence of side effects and adverse reactions when the drug is so prescribed (Petition at 53). You also assert that the drug may be considered misbranded because its label states its elimination half-life to be 4.5 hours, when Purdue has now indicated to you that the half-life is actually approximately 10 hours (Petition at 53).

Section 502 of the Federal Food, Drug, and Cosmetic Act provides that a drug will be considered misbranded if, among other things, the labeling for the product is false or misleading in any particular (21 U.S.C. 352). As discussed in this response, you have not provided the quantity and quality of scientific evidence to support your requested labeling changes regarding increased frequency of administration, and based on our independent analysis of the safety data, we believe that such labeling changes would be inappropriate. We therefore disagree that the labeling is false or misleading with respect to the issue of increased frequency of dosing and that in the absence of such information, OxyContin is misbranded.

With respect to your assertion that the drug product may be considered misbranded because the label states its elimination half-life to be 4.5 hours and Purdue has now indicated to you that the half-life is approximately 10 hours, we believe that your assertion fails to provide sufficient evidence that the drug product is misbranded. We note that the labeling for OxyContin was approved based on the data and studies provided in the NDA. Also, as we explained in section II.A.1 of this response, the half-life may vary because there can be considerable variability in a patient's absorption, metabolism, and excretion of the drug.

III. CONCLUSION

For the reasons discussed in this response, the information you have provided in the form of prescribing information, expert opinions, anecdotal evidence, and your analysis of MedWatch reports fails to support your conclusion that prescribing OxyContin at dosing intervals more frequent than q12h may increase the risk of side effects and serious adverse reactions. You also have not provided sufficient evidence to support your conclusion that dosing OxyContin at intervals more frequent than q12h may increase the potential for diversion or abuse of OxyContin. We therefore deny the requests for a black box warning, additional warnings and information in the labeling, and the issuance of a Dear Healthcare Professional letter, Safety Alert, Public Health Advisory, Talk Paper, or Urgent Notice.

Although we do not believe that an association has been demonstrated between prescribing OxyContin at dosing intervals more frequent than q12h and adverse events, we recognize that the possible misuse or abuse of OxyContin associated with issues other than frequency of dosing raise serious safety concerns. Since 1995 when OxyContin was approved, FDA has monitored and evaluated the safety concerns associated with OxyContin and has held meetings with Purdue,

Congress, other agencies, and convened Advisory Committees regarding such issues.[19] We will continue to closely monitor the safety of OxyContin and take actions as we believe appropriate.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[19] As an example, on May 5, 2008, FDA held a joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss NDA 22-272, OxyContin (oxycodone hydrochloride controlled-release) tablets for the proposed indication of management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. As stated in the meeting notice, the sustained-release characteristics of this formulation are purportedly less easily defeated than other formulations of OxyContin. See the March 27, 2008, *Federal Register* Notice (73 FR 16314).