CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022272 **COMPLETE RESPONSE**

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Craig Landau, M.D.
CMO & VP Clinical, Medical & Regulatory Affairs

Dear Dr. Landau:

Please refer to your new drug application (NDA) dated November 29, 2007, received November 29, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OxyContin (Oxycodone Hydrochloride Controlled-Release Tablets) 10, 15, 20, 30, 40 mg.

We acknowledge receipt of your amendments dated April 23, 2008, and March 30, May 18, June 2, 10, and 16, July 13 and 24, August 7, and September 18, October 6 and 9, November 6, 17, 19, and 23, and December 16 and 22, 2009.

The March 30, 2009, amendment constituted a complete response to our October 3, 2008, action letter, and included the addition of the 60- and 80-mg dosage strengths. However, you subsequently amended the application several times, including most recently on December 22, 2009, when you submitted a revised proposed Risk Evaluation and Mitigation Strategy (REMS).

We have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

As described in our letter dated December 11, 2009, in accordance with section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that a REMS is necessary for OxyContin to ensure that the benefits of the drug outweigh the risks of 1) use in non-opioid-tolerant individuals; 2) abuse; and 3) overdose, both accidental and intentional. We have determined that under section 505-1, the REMS for this product must include a Medication Guide and an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), and a timetable for submission of assessments. FDA cannot approve your application until we have found the content of your REMS acceptable.

We acknowledge the submission of your proposed REMS on December 22, 2009. Because the REMS was submitted so late in the review cycle, FDA is deferring its review of the REMS to the next cycle.

LABELING

We reserve additional comments on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

The Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) Panel, at the joint meeting on September 24, 2009, recommended that postmarketing studies be conducted to assess whether the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide deterrence of misuse and abuse actually result in a decrease in the serious risks of misuse and abuse, and their consequences: addiction, overdose and death.

FDA has determined that, if NDA 022272 is approved, you will be required to conduct postmarketing studies of OxyContin to assess the known serious risks of OxyContin, in particular, whether the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide deterrence of misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences, addiction, overdose and death.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the aforementioned risks

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 22272 is approved, you will be required pursuant to section 505(o)(3) of the FDCA to conduct the following:

> An epidemiological study (or studies) to address whether the changes made to the OxyContin formulation that are the subject of this application result in a decrease in misuse and abuse, and their consequences: overdose, death and addiction.

We acknowledge receipt of your proposals dated November 6 and December 16, 2009, containing your proposed brief outlines of possible postmarketing studies to fulfill this requirement. Because of design and feasibility challenges that we have noted in your proposal, we are concerned that the proposed studies will not successfully capture the necessary information that will allow us to assess the impact, if any, attributable to the change in the

OxyContin formulation. Therefore, additional information concerning the methodology and feasibility of the proposed potential studies, and possibly the addition of other studies, will be needed before agreement can be reached on the design of the postmarketing epidemiology study (or studies) that will assess the risks of reformulated OxyContin.

It will be necessary for you to complete methodology and feasibility assessments for the proposed studies. In addition, you should consider other potential outcome models for use in studying the risks associated with OxyContin, including but not limited to: accidental overdose in patients, medication errors resulting in adverse events involving the actions of healthcare providers or caregivers, unintentional overdose and/or poisoning in children, accidental overdose in recreational abusers, accidental overdose in experienced abusers, and patterns of abuse.

We will continue discussion of your postmarketing study proposals so that your complete response to this action letter contains adequately designed and acceptable studies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

We acknowledge that in a telephone conversation on December 7, 2009, you stated that you are (b) (4) We request that you submit the results of this study as soon as they become available.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, MD
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22272	ORIG-1	PURDUE PHARMA INC	OXYCONTIN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
12/30/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-272

COMPLETE RESPONSE

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Anthony C. Santopolo M.D.
Vice President, Regulatory Affairs

Dear Dr. Santopolo:

Please refer to your new drug application (NDA) dated November 29, 2007, received November 29, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OxyContin (Oxycodone Hydrochloride Controlled-Release Tablets), 10, 15, 20, 30, and 40 mg.

We acknowledge receipt of your amendments dated November 30, December 19, 20, and 21, 2007, and January 14, February 8, 12, 14 (2), and 15 (2), March 7, 10, 14, 18, 25 (2), and 27, April 11 and 23, May 7, and August 20, and September 26, 2008.

We also acknowledge receipt of your amendment dated April 23, 2008, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

1. Provide a new product name for the reformulated strengths if you intend to continue to market the original formulation at any strength at the same time as you intend to market the reformulated tablets. It is not acceptable to have some reformulated strength tablets and the same original formulation strength tablets available on the market at the same time with the same product name.

2. Provide studies of the new formulation that demonstrate the effects of physical and/or chemical manipulation and that incorporate the following:

a. The testing must be conducted in a blinded manner, preferably by an independent third party.

b. The methods used to assess the physical characteristics of the product must be reassessed. Consult individuals experienced in the intentional extraction of oxycodone from OxyContin for abuse to determine the methods for testing that will most likely replicate the methods encountered once the product is marketed. The resultant testing methods should then undergo a validation procedure to ensure they are conducted in a reproducible and meaningful manner.

c. Consult experts on extraction techniques to fully assess your proposed extraction testing protocols and to evaluate the data upon completion.

d. Provide data documenting the amount of oxycodone released if the reformulated tablet is chewed (b) (4)

e. Conduct studies to determine the relative rate of release of the active pharmaceutical ingredient from all strengths of crushed (b) (4) tablets to determine whether all dosage strengths retain the controlled-release properties after crushing (b) (4) and that dose dumping does not occur. (b) (4)

f. Provide data documenting how altering the grinding conditions, (b) (4) might affect the final particle size distribution of the tablets for all strengths and whether these efforts might render a product suitable for insufflation.

3. As noted during Division of Scientific Investigations inspection of Study OTR1005, accuracy of Period 1 oxycodone concentrations for subjects 5040-5042 in run 07307cga14a and subjects 5043, 5044, and 5046 in run 07307cgb14a cannot be assured. Therefore, before data from Study OTR1005 can be accepted, reanalyze and submit the data from study OTR1005 demonstrating bioequivalence after completely excluding data from subjects 5040, 5041, 5042, 5043, 5044, and 5045. Alternatively, reanalyze the plasma concentrations as identified and confirm the original values.

4. For the reasons described below, you must submit a proposed Risk Evaluation and Mitigation Strategy (REMS).

5. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

RISK EVALUATION AND MITIGATION STRATEGIES (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for OxyContin (Oxycodone Hydrochloride Controlled-Release Tablets) to ensure that the benefits of the drug outweigh the risks of: 1) use in non-opioid-tolerant individuals; 2) abuse; and 3) overdose, both accidental and intentional. We have determined that under section 505-1, the REMS for this product must include a Medication Guide, elements to assure safe use, an implementation system, and must include a timetable for assessments. You must submit a proposed REMS and REMS Supporting Document prior to final approval of this new drug application. You have been directed to prepare a REMS for the previously approved formulation of OxyContin NDA 20-553. You should review the elements of that REMS in preparing this proposed REMS for NDA 22-272.

Use the following designator to prominently label all submissions relating to this REMS:

NDA 22-272 PROPOSED REMS

ADDITIONAL COMMENTS

1. Serious consideration should be given to using a new trade name for the reformulated product, even if you do not intend to have the reformulated product available on the market at the same time as the current formulation. This would serve several purposes. First, it would give the context of a new product to support the new education program. Second, direct comparison as a "new and improved" OxyContin with the potential for a false sense of security would be avoided. Third, a novel name would permit national abuse monitoring and prescription databases to be able to track use and misuse of the new formulation immediately upon marketing and would avoid the situation of a transitional period with overlap of the two formulations during which time there could be no meaningful tracking of either product.

2. We strongly recommend that you submit all promotional material for review by the Agency prior to dissemination of the material. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

   Food and Drug Administration
   Center for Drug Evaluation and Research
   Division of Drug Marketing, Advertising, and Communications
   5901-B Ammendale Road
   Beltsville, MD 20705-1266

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission

must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lisa Basham, Regulatory Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bob Rappaport

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