# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-272**

# MEDICAL REVIEW(S)

**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**
**DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS**

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | December 30, 2009 |
| **From** | Bob A. Rappaport, M.D.<br>Director<br>Division of Anesthesia, Analgesia and Rheumatology Products |
| **Subject** | Division Director Summary Review |
| **NDA #** | 22-272 |
| **Applicant Name** | Purdue Pharma, L.P. |
| **Date of Submission** | March 31, 2009 (Response to CR letter) |
| **PDUFA Goal Date** | September 30, 2009; December 30, 2009 with clock extension |
| **Proprietary Name / Established (USAN) Name** | OxyContin® Tablets<br>Oxycodone hydrochloride controlled-release |
| **Dosage Forms / Strength** | Extended-release tablets<br>10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg |
| **Proposed Indication** | For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time |
| **Action:** | Complete Response |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | |
|---|---|
| Medical Officer Review | Jin Chen, M.D., Ph.D. |
| Statistical Review | (CMC only) Meiyu Shen, Ph.D.; Yi Tsong, Ph.D.; Stella Machado, Ph.D. |
| Pharmacology Toxicology Review | Elizabeth A. Bolan, Ph.D.; R. Daniel Mellon, Ph.D. |
| CMC Review | Craig M. Bertha, Ph.D.; Danae D. Christodoulou, Ph.D.; Ali Al-Hakim, Ph.D. |
| Microbiology Review | N/A |
| Clinical Pharmacology Review | Sayed Al Habet, R.Ph., Ph.D.; Suresh Doddapaneni, Ph.D. |
| DDMAC | Michelle Safarik, PA-C; Mathilda Fienkeng, Pharm.D.; Twyla Thompson, Pharm.D. |
| DSI | Jacqueline A. O'Shaughnessy, Ph.D.; C.T. Viswanathan, Ph.D. |
| CDTL Review | Ellen Fields, M.D.; Sharon Hertz, M.D. |
| CSS | James Tolliver, Ph.D.; Silvia Calderon, Ph.D.; Michael Klein, Ph.D. |
| OSE/DMEPA | Loretta Holmes, B.S.N., Pharm.D.; Kristina Arnwine, Pharm.D.; Denise Toyer, Pharm.D.; Carol Holquist, R.Ph. |
| OSE/DPVII | Afrouz Nayernama, Pharm.D. |
| OSE/DRISK | Jeane Perla, Ph.D.; Gita Toyserkani, Pharm.D.; Mary Willy, Ph.D.; Marcia Britt, Pharm.D.; Sharon Mills, B.S.N., R.N., C.C.R.P., Jodie Dickhorn, M.A.; Gerald Dal Pan, M.D. |
| DEPI | N/A |
| SEALD | Jeanne Delasko, RN, MS; Laurie Burke, R.Ph, M.P.H |
| Maternal Health Team | Richardae Araojo, Pharm.D.; Karen Feibus, M.D., Lisa Mathis, M.D. |
| Administrative Reviews/Letters | Lisa Basham, M.S.; Parinda Jani |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEDP=Division of Medication Error Prevention
DSI=Division of Scientific Investigations
DRISK= Division of Risk Management
DPVII=Division of Pharmacovigilance II
CDTL=Cross-Discipline Team Leader
DEPI= Division of Epidemiology
CSS=Controlled Substance Staff
SEALD=Study Endpoints and Labeling Development Team

# 1. Introduction

On November 29, 2007, Purdue Pharma, L.P. submitted a new drug application for their reformulated OxyContin tablets. This reformulation was undertaken to create tablets with controlled-release features that would be less easily compromised by tampering. The sponsor submitted data from a number of studies to support the new formulation's capacity to resist compromise of the controlled-release features. Based on our review of that application and the discussion of the application by a combined meeting of the Anesthetics and Life Support and the Drug Safety and Risk Management Advisory Committees on May 5, 2008, the sponsor received a Complete Response (CR) letter. The most significant inadequacies in the application were the poor quality of the studies submitted to support the sponsor's proposed labeling claims, the lack of an adequate REMS to assure that the benefits of the product outweigh its risks, and the sponsor's plan to market the 60 mg and 80 mg higher-strength tablets in the original formulation at the same time and with the same name that they marketed the lower-strength tablets in the new formulation. The Agency clearly informed the sponsor at their pre-NDA meeting that this plan would be unacceptable due to the potential for a misconception among prescribers that the higher-strength tablets would also have abuse-deterrent features. This misconception could lead to significant safety problems. The Agency's concern was strongly echoed by the Advisory Committee members. The October 3, 2008, CR letter delineated the following deficiencies that would need to be addressed by the sponsor in their response:

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, [redacted] (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).

The response submitted by Purdue on March 30, 2009 included updated CMC data for the reformulated 60 mg and 80 mg tablets, a genetic toxicology study to support a proposed labeling change, pharmacokinetic studies of the 60 mg and 80 mg strengths, and updated data regarding the tamper-resistant features of reformulated Oxycontin. On December 4, 2008, the Agency issued a letter to the sponsor informing them of the current efforts to develop a class-wide REMS and instructing them not to submit a REMS proposal until they received further guidance from the Agency. Therefore, a REMS proposal was not included in the sponsor's response to the Agency's October 3, 2008, CR letter. This review will focus only on the sponsor's response to the deficiencies outlined in the CR letter, and the need for a REMS and a post-marketing study to be defined as a Post-Marketing Requirement, as authorized under the Food and Drug Administration Amendments Act. All other details of the original application have been covered in my previous review which has been appended to this review.

## 2. Background

At the Agency's request, the sponsor did not submit a proposed REMS with this resubmission. On June 17, 2009, the Agency issued a REMS Notification Letter instructing the sponsor to submit a REMS proposal that included a Medication Guide, a Communication Plan, and a Timetable for Submission of Assessments. In response, the Sponsor submitted a REMS proposal on July 24, 2009. The REMS content was under negotiation and the sponsor submitted a REMS amendment to incorporate Agency changes on September 18, 2009. Due to the timing of this submission, the PDUFA review clock was extended by three months, providing for a new PDUFA date of December 30, 2009. Upon finalization of the review of the REMS proposal, the Agency determined that the REMS requirements would be changed to include a Medication Guide, Element to Assure Safe Use, specifically, healthcare provider training under 505-1(f)(3)(A), and a Timetable for Submission of Assessments, and issued a letter informing the sponsor of the change on December 11, 2009. The sponsor submitted their new REMS in response to this request on December 22, 2009, within a week of the action due date. With inadequate time for a thorough review of this new REMS, we will need to take a CR action at this time and review the new REMS as a response to the CR letter during the next review cycle. For additional background information see Appendix.

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.