

**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. Director 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 Oxycodone hydrochloride controlled-release |
| Dosage Forms / Strength | Extended-release tablets 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 | |
|------------------------------------|--|
| 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 Araujo, 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)
[REDACTED]
 - 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)
[REDACTED]

- 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).

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.

As the sponsor is now proposing to change all strengths of the OxyContin formulation at the same time, it is no longer necessary for the name to be changed.

3. CMC

Adequate data was submitted to support the quality, purity and stability of the reformulated 60 and 80 mg strength tablets. I concur with the CMC review team that no additional data is necessary for approval.

4. Nonclinical Pharmacology/Toxicology

Dr. Bolan reviewed the new in vitro chromosomal aberration assay in human peripheral blood lymphocytes conducted with oxycodone. The study showed that oxycodone did not produce clastogenicity. However, increased levels of polyploid cells were observed in cultures treated with oxycodone. The findings from this study will be described in the product label. I concur with the review team that no additional pharmacology or toxicology data is necessary for approval.

5. Clinical Pharmacology/Biopharmaceutics

The following has been reproduced from page 6 of Dr. Field's review:

The Applicant submitted three bioequivalence/dose-proportionality studies in the current application. Studies OTR1008 and OTR1009 demonstrated bioequivalence between a single 80mg dose of the reformulated Oxycontin and an 80mg dose of the currently marketed formulation in fed and fasted subjects, respectively. Study OTR1012 demonstrated the dose proportionality of 40mg, 60mg, and 80mg reformulated Oxycontin. Dose proportionality of the lower strengths including 40mg had been demonstrated during the first review cycle.

Per the Agency's complete response letter dated October 3, 2008, the Applicant reanalyzed the data from the bioequivalence Study OTR1005 of the 40mg strength after excluding six subjects that were included in the statistical analysis in the original NDA. This action was necessary to ensure accuracy of the bioequivalence data based on the DSI inspection report. The exclusion of these subjects from the analysis did not change the original conclusions that the 40mg reformulated Oxycontin is bioequivalent to the 40mg marketed formulation.

The Applicant also provided in vitro data that there was no effect of alcohol on the release rate of oxycodone from the 60mg and 80mg reformulated tablets. This plus the findings from the first cycle showing the same results for the 10mg through 40mg tablets confirms there is no evidence of dose dumping for this formulation at all proposed dosage strengths.

I concur with the clinical team that no additional clinical pharmacology data are necessary to support approval

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

No new efficacy data was required for or submitted with this response.

8. Safety

No new safety data was required for or submitted with this response. The only additional clinical experience was in the bioequivalence studies for which the subjects were naltrexone blocked and, thus, would not provide any meaningful safety experience to assess.

9. Advisory Committee Meeting

A joint meeting of the Anesthesia and Life Support and the Drug Safety and Risk Management Advisory Committees was held on September 19, 2009 to discuss the new data submitted to define the product's tamper-deterrent features. The committee members voted 14 to 4 with 1 abstention to approve the application. The consensus of the committee was that the reformulated product (all strengths) demonstrated an incremental increase in tamper-resistance, although it clearly maintained the previously acknowledged high risk for people who misused or abused the product by taking higher than safe doses of intact tablets. The advantages of the new formulation include:

- Perhaps most importantly, it cannot be crushed or chewed by standard mechanisms that may result in the ingestion of a lethal "immediate-release" dose by a casual or recreational abuser, or by a patient, e.g., when a nurse or caretaker attempts to crush and administer via a nasogastric tube.
- It cannot be altered to a consistency (i.e., powder) that can be insufflated or dissolved for injection using the standard household tools that the more hard-core abusers generally use.
- When dissolved in water it becomes a thick, gelatinous substance that cannot be syringed or injected with the usual needles and syringes used by hard-core abusers.

The committee members acknowledged that the reformulated OxyContin tablets can be crushed and/or extracted by unusual means and, therefore, those intent on abusing the products by defeating the extended-release mechanism will still be able to do so. The committee members also acknowledged that those abusing or misusing the product by ingesting more intact tablets or higher doses of intact tablets would not be provided with any protection from overdose with this reformulated product. Finally, the committee members were generally in consensus that a post-marketing epidemiology study to assess the impact of the reformulation on actual abuse in the community is essential to fully understand the value of the product and the level of risk management it will need, and that this study should be required as a post-marketing requirement for approval.


10. Pediatrics

Pediatric data was not submitted in this application and the application does not fall under the authority granted to FDA by PREA.


11. Other Relevant Regulatory Issues

The bulk of this submission consisted of the new studies performed to document the abuse-deterrent qualities of the new formulation. Dr. Tolliver of the Controlled Substances Staff provided a thorough review of those studies. The following is reproduced from page 7 of Dr. Fields' review and summarizes Dr. Tolliver's conclusions:

Detailed in vitro testing to characterize the tamper-resistant properties of reformulated Oxycontin was conducted on all dosage strengths. The reformulated Oxycontin may provide enhanced protection over that provided by the currently marketed Oxycontin for the intended population against dose dumping when tablets are accidentally crushed or chewed. (b) (4)

 (b) (4)

CSS determined that the Applicant's testing of the physicochemical attributes of the Oxycontin reformulation was adequate. The tamper-resistant properties will have no effect on abuse by the oral route (the most common mode of abuse), however there may some limited, incremental effect on abuse and misuse by other means. While the reformulation is harder to crush or chew, possibly mitigating some accidental misuse, oxycodone HCl is still relatively easily extracted (b) (4)



In general, the reformulated product should be viewed as an incremental improvement over the currently available Oxycontin

During the Open Public Hearing portion of the September 24, 2009 Advisory Committee meeting one of the speakers made several statements about additional risks associated with

(b) (4)



12. Labeling

The sponsor's proposed labeling has not been finalized on this review cycle.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

I concur with the review team and the advisory committee members that the sponsor has provided adequate data to demonstrate that their reformulated OxyContin product will potentially be more tamper-resistant based on changes to the controlled-release formulation, less likely to result in overdose when tampered with and ingested, and less likely to be insufflatable or syringeable/injectable. While this certainly does not solve the many problems associated with the misuse and abuse of OxyContin, it is an important incremental change. However, to fully support this approval, I again agree with the review team and the advisory committee members that the sponsor should be required to perform a post-marketing study to assess the impact of the new formulation in the community. This study should be undertaken as a Post-

Marketing Requirement under the authorities granted the Agency in the Food and Drugs Administration Amendments Act.

- Required Postmarketing Studies

Based on the available scientific data and the strong recommendation of the advisory committee members, FDA has determined that the sponsor must conduct an epidemiological study to address whether the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide misuse and abuse-deterrence actually result in a decrease in misuse and abuse, and their consequences, addiction, overdose and death, in the community. On December 16, 2009, the sponsor submitted a proposal for three studies to satisfy our request for this post-marketing requirement. The three studies proposed were:



No actual study design proposals were submitted and the brief descriptions of the studies were submitted within the last two weeks of the review cycle. On face, however, the proposed studies do not appear to be adequate to fully address the impact of the new formulation on misuse and abuse. We will continue to evaluate these proposed studies and, if necessary, require that the sponsor submit a new study design proposal with their response to the second CR letter so that they will, at the time of product approval, be able to provide a timetable according to which they will submit their final protocol, conduct their study and submit their final study report.

- Required Postmarketing Risk Evaluation and Mitigation Strategy

As I stated in my review of the original submission, an adequate REMS will be necessary to assure that the benefits of this product outweigh its risks, which are substantial. Based on the Agency's current efforts to develop a class REMS for long-acting or extended-release (such as this product) opioids and the fact that a number of these products are already approved and marketed with risk management programs of varying types, a decision was made to allow approval of new products that fall within this class with an interim REMS until the class REMS has been finalized. A letter was sent to the sponsor outlining this change in the requirements for their REMS on June 17, 2009. That letter stated

that they will be required to implement the class REMS when it is available. The letter noted that the interim REMS should consist of elements that are consistent with the currently existing risk management programs for the approved products that fall within this class, i.e., a MedGuide, a Communication Plan, and a Timetable for Submission of Assessments. The sponsor submitted their proposed REMS on July 24, 2009, based upon the requirements outlined in our letter, and submitted revisions based on Agency comments on September 18, 2009 and November 13, 2009. However, after further internal discussion and review of the proposed REMS, the Agency determined that the Medication Guide and Communication Plan will not be sufficient to ensure adequate training of healthcare providers to address the labeled risks of OxyContin and to prevent the occurrence of serious adverse events associated with those risks. Therefore, the interim REMS should not have a Communication Plan, but rather an Element to Assure Safe Use that would require prescriber education, in addition to the Medication Guide. The sponsor was sent a letter informing them of this change on December 11, 2009, and responded with their modified REMS on December 22, 2009. As this version of the REMS was submitted only one week before the action date for the application, there has not been adequate time for a thorough review. Therefore, we will not be able to approve this application at this time based on the absence of an agreed upon REMS.

APPENDIX

Summary Review, dated 9/30/2008 is included in its entirety as an individual document within this review.

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

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/s/

BOB A RAPPAPORT
12/30/2009



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, Building 22, 10903 New Hampshire Ave. Silver Spring MD 20993
Tel:(301)796-2280

Memo to NDA

DATE: December 30, 2009

TO: NDA 22-272 OxyContin
Submitted March 31, 2009

FROM: Sharon Hertz, M.D., Deputy Division Director

RE: Financial Disclosure

Introduction and Background

Purdue Pharma has submitted a Complete Response for their reformulated Oxycontin tablets. The original NDA was submitted on November 29, 2007, and Purdue was issued a Complete Response regulatory action on October 3, 2008.

The reformulated Oxycontin is intended to reduce the abuse liability of the product by making the modified-release characteristics more robust. The changes to the formulation are purported to result in a tablet that is more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means.

The original NDA submitted in 2007 consisted of CMC data, non-clinical pharmacology studies, pharmacokinetic studies, and studies that assessed the attributes of the reformulation in terms of the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product. During the development of the new formulation, the Applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent with the original formulation. As the new formulation had been demonstrated to be bioequivalent to the original formulation, no clinical efficacy or safety studies were performed.

The current Complete Response was submitted by Purdue on March 31, 2009 and included updated CMC data for the reformulated 60mg and 80mg tablets, genetic toxicology study to

support a proposed labeling change, pharmacokinetic studies of the 60mg and 80mg strengths, and updated data regarding abuse liability of reformulated Oxycontin.

A form 3454 was submitted on April 29, 2008 and documented that the applicant certified as to not having entered into any financial arrangement with the clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR54.2(a), and that none of the listed clinical investigators disclosed any proprietary interest in the product or company. In addition, no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR54.2(f). This documentation is adequate as it covers the necessary studies to support this application.

| 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/

SHARON H HERTZ
12/30/2009



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

**DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993**

Addendum to CDTL Review

DATE: December 30, 2009

NDA#: 22-272 Oxycontin Complete Response

Date of Submission: March 31, 2009

PDUFA date: December 30, 2009

FROM: Ellen Fields, M.D., M.P.H.
Clinical Team Leader
DAARP

My CDTL memo for this application which was entered into DAARTS on September 30, 2009, recommended a Complete Response regulatory action for this application based on the need for consensus between the Division and the Applicant regarding the postmarketing requirement for an epidemiologic study to assess the impact on abuse of the reformulated Oxycontin, and the lack of a final agreed-upon REMS. However, the decision was made by the Division on September 30, 2009 to extend the PDUFA clock since the submission of the final REMS would represent a major amendment to the NDA supplement.

Postmarketing Requirements

On December 16, 2009, the Applicant has submitted brief descriptions for three epidemiologic studies to assess the impact of the reformulation on the abuse of Oxycontin in the community. The proposed studies are as follows:



On face it appears that because of the design, methodological, and feasibility challenges noted in the proposal, there is concern that the proposed studies will not successfully capture the necessary safety information regarding the use of the reformulated OxyContin. Therefore, additional information concerning the methodology and feasibility of the proposed studies, as well as possible other studies, is needed before agreement can be reached on the design of the postmarketing epidemiology study (or studies) to address the safety profile of reformulated OxyContin. Agreement regarding the details of the conduct of the postmarketing epidemiologic studies is not required pre-approval, however at the time of approval, a timetable must be agreed upon for submission of the final protocols, the dates for starting and completing the studies, and the dates of submission to the Agency of the final study reports.

REMS

Although the Agency initially determined that an adequate REMS for this product (an interim or “place-holding” REMS until the class-wide opioid REMS is put in place) would consist of a Medication Guide and Communication plan, a decision was subsequently made that this plan will not be adequate to ensure training of healthcare professionals to address the labeled risks of abuse, misuse, overdose, and addiction, and to prevent the occurrence of serious adverse events associated with those risks. To that end, a letter was issued to the Applicant on December 11, 2009 stating that the Agency has determined that the REMS for OxyContin (oxycodone hydrochloride) should contain an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), to ensure that the benefits of OxyContin (oxycodone hydrochloride) outweigh the risks. The REMS must include a Medication Guide, elements to assure safe use,

specifically training of healthcare providers, and a timetable for the submission of assessments of the REMS.

The Elements to Assure Safe Use must include, at a minimum, the following:

- 1) A plan to ensure that OxyContin (oxycodone hydrochloride) will only be prescribed by healthcare providers who have particular training under 505-1(f)(3)(A) about the information described below. At a minimum the plan shall require that:
 - (a) Healthcare providers are trained about:
 - (i) Proper patient selection
 - (ii) Appropriate product dosing and administration
 - (iii) General opioid use including information about opioid abuse and how to identify patients who are at risk for addiction
 - (iv) The risks of abuse, misuse, overdose, and addiction from exposure to opioids, including OxyContin (oxycodone hydrochloride)
 - (v) The risks of OxyContin (oxycodone hydrochloride) including:
 1. The risk of overdose caused by exposure to an essentially immediate-release form of oxycodone due to broken, chewed crushed or dissolved OxyContin (oxycodone hydrochloride)
 2. The risk of addiction from exposure to OxyContin (oxycodone hydrochloride)

(b) (4)

 - (vi) Information to counsel patients on the need to store opioid analgesics safely out of reach of children and household acquaintances
 - (vii) The importance of providing each patient a Medication Guide with each prescription and instructing the patient to read it.
- (b) Healthcare providers will be retrained periodically, at a specified interval.

Information needed for assessment of the REMS may include but may not be limited to:

- a. An evaluation of patients' understanding of the serious risks of OxyContin (oxycodone hydrochloride).
- b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- d. A report on the status of the training program for healthcare providers.
- e. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with OxyContin (oxycodone hydrochloride) (for example, through surveys of healthcare providers).

- f. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
- g. An analysis and summary of surveillance and monitoring activities for abuse, misuse and overdose, and any intervention taken resulting from signals of abuse, misuse and overdose.
- h. A claims study to evaluate OxyContin (oxycodone hydrochloride) utilization patterns including opioid-tolerant utilization patterns before and after implementation of the REMS.
- i. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

The Applicant submitted their proposed revised REMS on December 22, 2009. Because the REMS was submitted so late in the review cycle, the Agency is deferring its review of the REMS to the next cycle.

Other Regulatory Issues

The following is extracted directly from Dr. Rappaport's Division Director Summary.

During the open public hearing of the September 24, 2009 Advisory Committee meeting, an individual made several statements about risk

(b) (4)



Recommendation for Regulatory Action**Complete Response**

Please refer to my CDTL memo dated September 30, 2009 (attached) for details regarding the risk/benefit analysis.

Deficiency

1. FDA cannot approve this application until the content of the REMS is found to be acceptable.

Information Needed to Address Deficiency

1. The Division acknowledges the submission of the proposed REMS on December 22, 2009 and because it was submitted so late in the review cycle, the review is being deferred to the next cycle.
- 2.

Postmarketing Requirements

A postmarketing epidemiologic study(ies) is required to assess whether changes made to the Oxycontin formulation that are intended to provide misuse and abuse-deterrence actually result in a decrease in the risks of abuse and misuse, and their consequences including addiction, overdose, and death in the community.

Cross-Discipline Team Leader Review

| | |
|--|--|
| Date | September 29, 2009 |
| From | Ellen W. Fields, M.D., M.P.H. |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 22-272 Complete Response |
| Supplement# | |
| Applicant | Purdue Pharma |
| Date of Submission | March 31, 2009 |
| PDUFA Goal Date | September 30, 2009 |
| Proprietary Name / Established (USAN) names | Oxycontin/ Controlled-Release Oxycodone |
| Dosage forms / Strength | Tablets 10, 15, 20, 30, 40, 60, and 80mg |
| Proposed Indication(s) | For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time |
| Recommended: | Complete Response |

| | |
|------------------------------------|--|
| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Clinical Pharmacology Review | Sayed Al Habet, R.Ph, Ph.D. Suresh Doddapaneni, Ph.D. |
| Pharmacology Toxicology Review | Elizabeth Bolan, Ph.D. Daniel Mellon, Ph.D. |
| CMC Review | Craig Bertha, Ph.D. Ali Al-Hakim, Ph.D. |
| OSE/DRISK | Jeanne Pearla, Ph.D. |
| CSS | James Tolliver, Ph.D. |

Introduction and Background

Purdue Pharma has submitted a Complete Response for their reformulated Oxycontin tablets. The original NDA was submitted on November 29, 2007, and Purdue was issued a Complete Response regulatory action on October 3, 2008.

Oxycontin is a modified-release formulation of oxycodone that was initially approved December 12, 1995 as 10 mg, 20 mg, and 40 mg tablets. An 80 mg tablet was approved January 6, 1997, followed by a 160 mg tablet on March 15, 2000, and 15 mg, 30 mg and 60 mg tablets on September 18, 2006. The Applicant ceased distribution of the 160 mg tablet in April of 2001.

The reformulated Oxycontin is intended to reduce the abuse liability of the product by making the modified-release characteristics more robust. The changes to the formulation are purported to result in a tablet that is more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means.

The original NDA submitted in 2007 consisted of CMC data, non-clinical pharmacology studies, pharmacokinetic studies, and studies that assessed the attributes of the reformulation in terms of the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product. During the development of the new formulation, the Applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent with the original formulation. As the new formulation had been demonstrated to be bioequivalent to the original formulation, no studies were performed.

The proposed indication for the reformulated Oxycontin is the same as the already marketed version. The Applicant's intention at the time of the original NDA submission was to market the 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg as the reformulated Oxycontin, and continue to market the 60 mg and 80 mg as the original, unreformulated Oxycontin, until such a time as they were able to reformulate the higher strengths. Prior to Purdue submitting the NDA, the Division expressed concern that the reformulated lower-strength tablets should not be marketed at the same time as the original higher-strength tablets, due to the risk of misconceptions and the resultant medication errors that might occur,

(b) (4)



In order to provide some additional incentive to sponsors, the Agency would consider allowing limited data from studies that evaluated the abuse-resistant features of the products to be added to appropriate sections of the product label.

As this was the first NDA submission of an abuse-resistant opioid formulation, the Agency felt that it was essential that the application be discussed at a joint public meeting of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees. The joint committee meeting was held on May 5, 2008. The general consensus of the committee members was that the quality of the data related to the formulation's "abuse-resistance" presented by the sponsor was wholly inadequate to support their contention that the formulation changes would provide any reduction in abuse of the product.

Please refer to Dr. Sharon Hertz's CDTL/Deputy Director memo of the original NDA submission for a summary of the May 5, 2008 Advisory Committee meeting for additional details regarding the conclusions reached by the Committees.

As stated in Dr. Bob Rappaport's Summary Review for Regulatory Action dated September 30, 2008, "Therefore, while the physiochemical changes in this new formulation of Oxycontin might provide an incremental decrease in the ability of abusers to compromise the controlled-release component, the sponsor has not provided data that has been obtained in a rigorously scientific manner to support this claim and I am unable to make a thorough risk-benefit assessment in the absence of quality data. I also remain concerned that the data that was collected shows a potential for serious adverse events to occur due to the limited and poor

quality documentation of the variability in the quantity of oxycodone that will be released after manipulation of the controlled-release features. Given the previous behavior exhibited by the sponsor, it is essential that they employ the highest level of scientific rigor, and document a clear absence of potential bias, before I would be able to accept their data in support of even an implicit claim of increased abuse resistance. The implication of some improvement in abuse resistance that would be tied to approval of this formulation, whether or not we allow minimal or even no information to be added to the product label regarding the changes to the formulation or the results of the studies, could lead to inappropriate prescribing of the product due to misconceptions about its abuse-resistant qualities.”

Additionally, Dr. Rappaport noted in his review that it is essential that simultaneously marketed Oxycontin tablets of different strengths are all of the same formulation. The risks of having different formulations include dosing errors likely accompanied by overdoses and significant morbidity and mortality.

A Complete Response was issued to Purdue on October 3, 2008, and included the following reasons for the action and recommendations to address them:

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)
(b) (4)
 - f. Provide data documenting how altering the grinding conditions, (b) (4) (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.

In addition, the Applicant was told to submit proposed REMS with the resubmission of the NDA.

The Complete Response submitted by Purdue on March 31, 2009 included updated CMC data for the reformulated 60mg and 80mg tablets, genetic toxicology study to support a proposed labeling change, pharmacokinetic studies of the 60mg and 80mg strengths, and updated data regarding abuse liability of reformulated Oxycontin.

CMC/Device

The primary CMC review was performed by Dr. Craig Bertha with supervisory concurrence from Dr. Ali Al-Hakim.

The drug product is Oxycontin (oxycodone hydrochloride controlled-release) Tablets in proposed strengths of 10, 15, 20, 30, 40, 60, and 80mg/tablet. The only substantial difference between CMC data submitted in the original NDA submission and this submission is that the Applicant has reformulated the 60 mg and 80 mg tablets, so that now all strengths are reformulated. Dr. Bertha's review focused mainly on the new higher strengths.

An information request regarding the 60mg and 80mg strengths, dated May 1, 2009, was sent to the Applicant, who responded on May 13, 2009. In that response, the Applicant provided necessary information regarding the master batch record for the 60mg and 80mg strength tablets. Although the validation of these higher strengths was not complete, updated manufacturing details were provided. Dr. Bertha found the response acceptable since process validation at full commercial scale often takes place post approval.

Justification of the limit for (b) (4) in the polyethylene oxide excipient of nmt (b) (4) (above ICH Q3C guideline threshold) was provided with acceptance criteria, and found acceptable by both Dr. Bertha and the non-clinical review team. Additional requests included labeling revisions which were also found acceptable.

The Applicant provided updated 18 and 24-month long-term stability data for product strengths 10–40 mg, and 24-month stability data for the 60 and 80 mg strengths. The statistician analyzed the updated assay and dissolution stability data for all strengths and concluded that the 24-month expiry is acceptable.

The CMC review team recommended that in order to be compliant with current ONDQA policy, the applicant change the drug product established name to “oxycodone hydrochloride extended release tablets” from “oxycodone hydrochloride controlled-release tablets.” However, in order to not create confusion for prescribers and patients regarding this new formulation, the name will not be changed at this time.

There are no CMC findings that preclude approval of this application.

Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was performed by Elizabeth Bolan, Ph.D., with supervisory concurrence from Dan Mellon, Ph.D. The following summarizes significant findings from her review. Dr. Bolan also completed the preclinical review for the first cycle of this NDA.

There were no preclinical approvability issues during the first cycle of this NDA. The current submission contained one genetic toxicology study to support a proposed labeling change. Also, as stated in the CMC section above, the preclinical team was in agreement with the Applicant's justification regarding the (b) (4) specification.

Dr. Bolan reviewed Study # 778436, an in vitro chromosomal aberration assay in human peripheral blood lymphocytes conducted with oxycodone. The study showed that oxycodone did not produce clastogenicity. However, increased levels of polyploid cells were observed in cultures treated with oxycodone. The findings from this study will be described in the product label.

Labeling recommendations included changes to Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. Details of these changes may be found in Dr. Bolan's review.

No new non-clinical safety issues were identified during this review cycle, and there are no nonclinical findings that preclude approval of this application.

Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review was performed by Dr. Sayed Al Habet with supervisory concurrence from Dr. Suresh Doddapaneni.

The Applicant submitted three bioequivalence/dose-proportionality studies in the current application. Studies OTR1008 and OTR1009 demonstrated bioequivalence between a single 80mg dose of the reformulated Oxycontin and an 80mg dose of the currently marketed formulation in fed and fasted subjects, respectively. Study OTR1012 demonstrated the dose proportionality of 40mg, 60mg, and 80mg reformulated Oxycontin. Dose proportionality of the lower strengths including 40mg had been demonstrated during the first review cycle.

Per the Agency's complete response letter dated October 3, 2008, the Applicant reanalyzed the data from the bioequivalence Study OTR1005 of the 40mg strength after excluding six subjects that were included in the statistical analysis in the original NDA. This action was necessary to ensure accuracy of the bioequivalence data based on the DSI inspection report. The exclusion of these subjects from the analysis did not change the original conclusions that the 40mg reformulated Oxycontin is bioequivalent to the 40mg marketed formulation.

The Applicant also provided in vitro data that there was no effect of alcohol on the release rate of oxycodone from the 60mg and 80mg reformulated tablets. This plus the findings from the first cycle showing the same results for the 10mg through 40mg tablets confirms there is no evidence of dose dumping for this formulation at all proposed dosage strengths.

There are no Clinical Pharmacology findings that preclude approval of this application.

Clinical/Statistical- Efficacy/Safety

During the development of the new formulation, the Applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent to the original formulation. As the new formulation has been demonstrated to be bioequivalent to the original formulation, no studies were performed. The only safety data submitted in this application was from pharmacokinetic studies where the subjects were naltrexone blocked. These studies do not provide additional safety information related to Oxycontin.




Attributes of the Formulation/Abuse Liability

As noted previously in this memo, the Complete Response letter sent to the Applicant requested additional physicochemical testing of the reformulated tablets due to lack of

scientific rigor and adequate methodology of these studies in the original NDA submission. In response, the Applicant provided detailed information on in vitro studies conducted to evaluate the tamper-resistant characteristics of the reformulated tablets, including the 60 and 80 mg strengths, with comparison to the tamper resistant characteristics of the currently available Oxycontin.

An extensive review of these studies has been completed by Dr. James Tolliver of the Controlled Substances Staff (CSS), with supervisory concurrence by Drs. Silvia Calderone and Michael Klein. What follows is a brief summary of Dr. Tolliver's conclusions.

Detailed in vitro testing to characterize the tamper-resistant properties of reformulated Oxycontin was conducted on all dosage strengths. The reformulated Oxycontin may provide enhanced protection over that provided by the currently marketed Oxycontin for the intended population against dose dumping when tablets are accidentally crushed or chewed. (b) (4)



CSS determined that the Applicant's testing of the physicochemical attributes of the Oxycontin reformulation was adequate. The tamper-resistant properties will have no effect on abuse by the oral route (the most common mode of abuse), however there may some limited, incremental effect on abuse and misuse by other means. While the reformulation is harder to crush or chew, possibly mitigating some accidental misuse, oxycodone HCl is still relatively easily extracted (b) (4)

In general, the reformulated product should be viewed as an incremental improvement over the currently available Oxycontin

Advisory Committee Meeting

A combined meeting of the ALSDAC and DSaRM Advisory Committees was held on September 24, 2009 in order to provide guidance to the Agency regarding the adequacy of the

Applicant's rigor used to assess the abuse liability of the reformulated Oxycontin, and to discuss the overall safety of the new formulation. The following questions were asked of the committee members:

1. Were the studies performed by the sponsor adequate to provide data on the abuse-deterrent characteristics of the reformulated Oxycontin product?
2. Does the change in formulation affect the overall safety profile of Oxycontin?
3. Should this application for reformulated Oxycontin be approved?

The general consensus of the Committees was that the studies performed by the Applicant were adequate to provide data regarding the physicochemical abuse deterrent characteristics of the reformulated Oxycontin, and that these characteristics provide an incremental improvement in the overall safety profile of the product. The predominant improvement of the reformulation is that it is extremely difficult to chew or crush, thereby decreasing the likelihood of a patient accidentally chewing the pill and defeating the extended-release characteristics of the formulation, a caregiver crushing the pill to administer via a G-tube, or a non-experienced abuser intentionally chewing the pill to obtain a quicker high. The Committees recognized that these situations constitute a small proportion of the methods of Oxycontin abuse or misuse, the majority being oral administration of an intact tablet, snorting, and injection. The Sponsor maintained that because it is more difficult (but not impossible) to extract oxycodone from the reformulated product (b) (4), compared to the original Oxycontin, snorting and injection may also be affected by the change in formulation. The committee was not convinced of this since although the extraction of oxycodone is more difficult than with the original Oxycontin, it is possible with (b) (4).

The Committees felt strongly that the reformulated Oxycontin should be approved only if there is a post-marketing requirement for an epidemiologic study to assess the impact of the reformulation on the abuse of Oxycontin in the community. This is the type of study that the Division and many in the pain/addiction community have viewed as very important to fully assess the impact of the new "abuse-deterrent" opioid formulations. To this end, the Sponsor will be required to submit a proposal for the design of such a study prior to approval.

Other Relevant Regulatory Issues

None

Labeling

The name of the product will continue to be Oxycontin/ oxycodone hydrochloride controlled-release tablets. Labeling changes to the current label are minimal, and include updates in the preclinical and clinical pharmacology sections. A Medication Guide has been developed to better mitigate the risks associated with Oxycontin, and will be part of the REMS described below. There will be no information in the label regarding the physicochemical attributes of the formulation or claims regarding tamper or abuse-resistance. At this writing, discussions regarding labeling are ongoing with the Applicant.

Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action and Risk Benefit Assessment

I recommend a Complete Response action for the reformulated Oxycontin because of the consensus of the Division and the members of the September 24, 2009 Advisory Committees that there be a post-marketing requirement for an epidemiologic study to assess the effect of the reformulated product on the abuse of Oxycontin as a condition of approval. The Applicant has satisfactorily responded to the deficiencies communicated in the Complete Response Action of October 3, 2008. They are planning to market all strengths as reformulated Oxycontin, and have provided sufficient data to do so. The abuse liability studies appear to have been conducted with adequate rigor. While it is clear from the results of the in vitro abuse liability studies that this formulation will not be a panacea for abuse of Oxycontin, nor is it completely abuse “resistant”, it does appear to convey an incremental improvement over the marketed Oxycontin in terms of “tamperability”. The true “abuse resistance” of this formulation can only be determined by long-term epidemiologic studies of rates of abuse in the community.

In order to mitigate the risks of abuse, misuse, overdose and addiction, a REMS will be implemented upon approval of this product. Oxycontin, as an extended-release opioid, will become part of the class-wide REMS for these products currently under development. In the meantime, an interim REMS, described below, will be put in place until required elements of the class-wide REMS have been determined. The Agency has made a determination that approvals of extended release opioids should not be delayed while the development of the class-wide REMS is in progress, as long as the safety profile of the drug is not worse than the currently marketed long-acting opioids. For these drugs, an “interim REMS” will be implemented until the class-wide REMS is finalized. The reformulated Oxycontin is expected to have the same safety profile as the currently marketed product, and therefore falls into this category.

- Recommendation for Postmarketing Risk Management Activities

As determined during the first review cycle, a Risk Mitigation and Evaluation Strategy must exist for Oxycontin to address the risks of abuse, misuse, overdose, and addiction. Since Oxycontin belongs to the class of extended-release opioid products, the REMS currently in development for these drugs must also be adopted by the Applicant. Until that occurs, the Agency has determined that an “interim REMS” must be put into place until the class-wide REMS is implemented. Once the necessary elements of the class-wide REMS are determined, the Applicant will be notified in writing and will be required to submit a modified REMS to incorporate those elements.

The request for an interim REMS, sent to the Applicant on June 17, 2009, included the following requirements:

1. Medication Guide
2. Communication Plan
 - To include educational materials for prescribers that address proper patient selection, dosing and administration, general information

regarding opioid abuse, misuse and addiction, risks of Oxycontin, and proper storage in order to keep drug away from children.

- A description of the audience for the communication plan must be included, as well as a schedule for how and when the plan's materials are to be distributed.

3. A Timetable For Submission Of Assessments

Additional details regarding the above requirements are discussed in Dr. Hertz's CDTL memo from the first review cycle.

As requested, the Applicant submitted an interim REMs that included the above elements. The Communication Plan consists of a Dear Prescriber Letter, Dear Pharmacist Letter, and a brochure entitled "Prescribing Oxycontin: A Healthcare Professional Guide".

The review of the elements of the REMS (conducted by DAARP, OSE (DRISK), DMETS, and the Office of Compliance) and discussions with the Applicant regarding the REMS are currently in their final stages.

- Recommendation for other Postmarketing Study Commitments

The Applicant is required to perform an epidemiologic study to assess the impact of the reformulation on the abuse of Oxycontin in the community. To that end, the Applicant must submit a proposal presenting the design of such a study prior to approval.

- Recommended Comments to Applicant

The following comments will be conveyed to the Applicant in the Complete Response Letter:

1. We request that you propose a study and/or clinical trial to address the following issue:

Will the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide misuse and abuse-deterrence actually result in a decrease in misuse and abuse, and their consequences, addiction, overdose and death, in the community.

2. Submit your protocol proposal and a timetable according to which you are going to conduct your study.
3. You must submit an acceptable REMS and REMS Supporting Document prior to final approval of this new drug application.

| 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/

ELLEN W FIELDS
12/30/2009

Cross-Discipline Team Leader Review

| | |
|--|--|
| Date | September 29, 2009 |
| From | Ellen W. Fields, M.D., M.P.H. |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 22-272 Complete Response |
| Supplement# | |
| Applicant | Purdue Pharma |
| Date of Submission | March 31, 2009 |
| PDUFA Goal Date | September 30, 2009 |
| Proprietary Name / Established (USAN) names | Oxycontin/ Controlled-Release Oxycodone |
| Dosage forms / Strength | Tablets 10, 15, 20, 30, 40, 60, and 80mg |
| Proposed Indication(s) | For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time |
| Recommended: | Complete Response |

| | |
|------------------------------------|--|
| Material Reviewed/Consulted | |
| OND Action Package, including: | |
| Clinical Pharmacology Review | Sayed Al Habet, R.Ph, Ph.D. Suresh Doddapaneni, Ph.D. |
| Pharmacology Toxicology Review | Elizabeth Bolan, Ph.D. Daniel Mellon, Ph.D. |
| CMC Review | Craig Bertha, Ph.D. Ali Al-Hakim, Ph.D. |
| OSE/DRISK | Jeanne Pearla, Ph.D. |
| CSS | James Tolliver, Ph.D. |

Introduction and Background

Purdue Pharma has submitted a Complete Response for their reformulated Oxycontin tablets. The original NDA was submitted on November 29, 2007, and Purdue was issued a Complete Response regulatory action on October 3, 2008.

Oxycontin is a modified-release formulation of oxycodone that was initially approved December 12, 1995 as 10 mg, 20 mg, and 40 mg tablets. An 80 mg tablet was approved January 6, 1997, followed by a 160 mg tablet on March 15, 2000, and 15 mg, 30 mg and 60 mg tablets on September 18, 2006. The Applicant ceased distribution of the 160 mg tablet in April of 2001.

The reformulated Oxycontin is intended to reduce the abuse liability of the product by making the modified-release characteristics more robust. The changes to the formulation are purported to result in a tablet that is more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means.

The original NDA submitted in 2007 consisted of CMC data, non-clinical pharmacology studies, pharmacokinetic studies, and studies that assessed the attributes of the reformulation in terms of the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product. During the development of the new formulation, the Applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent with the original formulation. As the new formulation had been demonstrated to be bioequivalent to the original formulation, no studies were performed.

The proposed indication for the reformulated Oxycontin is the same as the already marketed version. The Applicant's intention at the time of the original NDA submission was to market the 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg as the reformulated Oxycontin, and continue to market the 60 mg and 80 mg as the original, unreformulated Oxycontin, until such a time as they were able to reformulate the higher strengths. Prior to Purdue submitting the NDA, the Division expressed concern that the reformulated lower-strength tablets should not be marketed at the same time as the original higher-strength tablets, due to the risk of misconceptions and the resultant medication errors that might occur,

(b) (4)



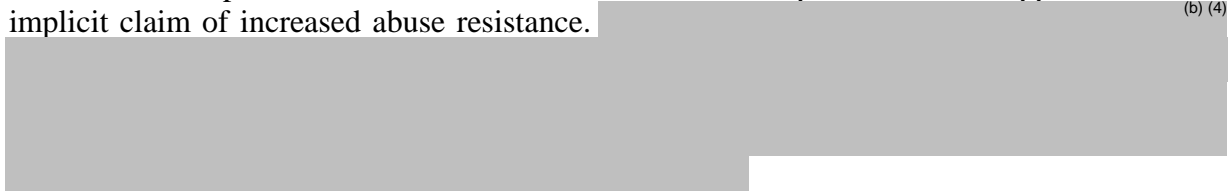
In order to provide some additional incentive to sponsors, the Agency would consider allowing limited data from studies that evaluated the abuse-resistant features of the products to be added to appropriate sections of the product label.

As this was the first NDA submission of an abuse-resistant opioid formulation, the Agency felt that it was essential that the application be discussed at a joint public meeting of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees. The joint committee meeting was held on May 5, 2008. The general consensus of the committee members was that the quality of the data related to the formulation's "abuse-resistance" presented by the sponsor was wholly inadequate to support their contention that the formulation changes would provide any reduction in abuse of the product.

Please refer to Dr. Sharon Hertz's CDTL/Deputy Director memo of the original NDA submission for a summary of the May 5, 2008 Advisory Committee meeting for additional details regarding the conclusions reached by the Committees.

As stated in Dr. Bob Rappaport's Summary Review for Regulatory Action dated September 30, 2008, "Therefore, while the physiochemical changes in this new formulation of Oxycontin might provide an incremental decrease in the ability of abusers to compromise the controlled-release component, the sponsor has not provided data that has been obtained in a rigorously scientific manner to support this claim and I am unable to make a thorough risk-benefit assessment in the absence of quality data. I also remain concerned that the data that was collected shows a potential for serious adverse events to occur due to the limited and poor

quality documentation of the variability in the quantity of oxycodone that will be released after manipulation of the controlled-release features. Given the previous behavior exhibited by the sponsor, it is essential that they employ the highest level of scientific rigor, and document a clear absence of potential bias, before I would be able to accept their data in support of even an implicit claim of increased abuse resistance. (b) (4)



Additionally, Dr. Rappaport noted in his review that it is essential that simultaneously marketed Oxycontin tablets of different strengths are all of the same formulation. The risks of having different formulations include dosing errors likely accompanied by overdoses and significant morbidity and mortality.

A Complete Response was issued to Purdue on October 3, 2008, and included the following reasons for the action and recommendations to address them:

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 and (b) (4) tablets to determine whether all dosage strengths retain the controlled-release properties after crushing and (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.

In addition, the Applicant was told to submit proposed REMS with the resubmission of the NDA.

The Complete Response submitted by Purdue on March 31, 2009 included updated CMC data for the reformulated 60mg and 80mg tablets, genetic toxicology study to support a proposed labeling change, pharmacokinetic studies of the 60mg and 80mg strengths, and updated data regarding abuse liability of reformulated Oxycontin.

CMC/Device

The primary CMC review was performed by Dr. Craig Bertha with supervisory concurrence from Dr. Ali Al-Hakim.

The drug product is Oxycontin (oxycodone hydrochloride controlled-release) Tablets in proposed strengths of 10, 15, 20, 30, 40, 60, and 80mg/tablet. The only substantial difference between CMC data submitted in the original NDA submission and this submission is that the Applicant has reformulated the 60 mg and 80 mg tablets, so that now all strengths are reformulated. Dr. Bertha's review focused mainly on the new higher strengths.

An information request regarding the 60mg and 80mg strengths, dated May 1, 2009, was sent to the Applicant, who responded on May 13, 2009. In that response, the Applicant provided necessary information regarding the master batch record for the 60mg and 80mg strength tablets. Although the validation of these higher strengths was not complete, updated manufacturing details were provided. Dr. Bertha found the response acceptable since process validation at full commercial scale often takes place post approval.

Justification of the limit for (b) (4) in the polyethylene oxide excipient of nmt (b) (4) (above ICH Q3C guideline threshold) was provided with acceptance criteria, and found acceptable by both Dr. Bertha and the non-clinical review team. Additional requests included labeling revisions which were also found acceptable.

The Applicant provided updated 18 and 24-month long-term stability data for product strengths 10–40 mg, and 24-month stability data for the 60 and 80 mg strengths. The statistician analyzed the updated assay and dissolution stability data for all strengths and concluded that the 24-month expiry is acceptable.

The CMC review team recommended that in order to be compliant with current ONDQA policy, the applicant change the drug product established name to “oxycodone hydrochloride extended release tablets” from “oxycodone hydrochloride controlled-release tablets.” However, in order to not create confusion for prescribers and patients regarding this new formulation, the name will not be changed at this time.

There are no CMC findings that preclude approval of this application.

Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review was performed by Elizabeth Bolan, Ph.D., with supervisory concurrence from Dan Mellon, Ph.D. The following summarizes significant findings from her review. Dr. Bolan also completed the preclinical review for the first cycle of this NDA.

There were no preclinical approvability issues during the first cycle of this NDA. The current submission contained one genetic toxicology study to support a proposed labeling change. Also, as stated in the CMC section above, the preclinical team was in agreement with the Applicant's justification regarding the isopentane specification.

Dr. Bolan reviewed Study # 778436, an in vitro chromosomal aberration assay in human peripheral blood lymphocytes conducted with oxycodone. The study showed that oxycodone did not produce clastogenicity. However, increased levels of polyploid cells were observed in cultures treated with oxycodone. The findings from this study will be described in the product label.

Labeling recommendations included changes to Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. Details of these changes may be found in Dr. Bolan's review.

No new non-clinical safety issues were identified during this review cycle, and there are no nonclinical findings that preclude approval of this application.

Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review was performed by Dr. Sayed Al Habet with supervisory concurrence from Dr. Suresh Doddapaneni.

The Applicant submitted three bioequivalence/dose-proportionality studies in the current application. Studies OTR1008 and OTR1009 demonstrated bioequivalence between a single 80mg dose of the reformulated Oxycontin and an 80mg dose of the currently marketed formulation in fed and fasted subjects, respectively. Study OTR1012 demonstrated the dose proportionality of 40mg, 60mg, and 80mg reformulated Oxycontin. Dose proportionality of the lower strengths including 40mg had been demonstrated during the first review cycle.

Per the Agency's complete response letter dated October 3, 2008, the Applicant reanalyzed the data from the bioequivalence Study OTR1005 of the 40mg strength after excluding six subjects that were included in the statistical analysis in the original NDA. This action was necessary to ensure accuracy of the bioequivalence data based on the DSI inspection report. The exclusion of these subjects from the analysis did not change the original conclusions that the 40mg reformulated Oxycontin is bioequivalent to the 40mg marketed formulation.

The Applicant also provided in vitro data that there was no effect of alcohol on the release rate of oxycodone from the 60mg and 80mg reformulated tablets. This plus the findings from the first cycle showing the same results for the 10mg through 40mg tablets confirms there is no evidence of dose dumping for this formulation at all proposed dosage strengths.

There are no Clinical Pharmacology findings that preclude approval of this application.

Clinical/Statistical- Efficacy/Safety

During the development of the new formulation, the Applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent to the original formulation. As the new formulation has been demonstrated to be bioequivalent to the original formulation, no studies were performed. The only safety data submitted in this application was from pharmacokinetic studies where the subjects were naltrexone blocked. These studies do not provide additional safety information related to Oxycontin.


Attributes of the Formulation/Abuse Liability

As noted previously in this memo, the Complete Response letter sent to the Applicant requested additional physicochemical testing of the reformulated tablets due to lack of

scientific rigor and adequate methodology of these studies in the original NDA submission. In response, the Applicant provided detailed information on in vitro studies conducted to evaluate the tamper-resistant characteristics of the reformulated tablets, including the 60 and 80 mg strengths, with comparison to the tamper resistant characteristics of the currently available Oxycontin.

An extensive review of these studies has been completed by Dr. James Tolliver of the Controlled Substances Staff (CSS), with supervisory concurrence by Drs. Silvia Calderone and Michael Klein. What follows is a brief summary of Dr. Tolliver's conclusions.

Detailed in vitro testing to characterize the tamper-resistant properties of reformulated Oxycontin was conducted on all dosage strengths. The reformulated Oxycontin may provide enhanced protection over that provided by the currently marketed Oxycontin for the intended population against dose dumping when tablets are accidentally crushed or chewed. (b) (4)

 (b) (4)

CSS determined that the Applicant's testing of the physicochemical attributes of the Oxycontin reformulation was adequate. The tamper-resistant properties will have no effect on abuse by the oral route (the most common mode of abuse), however there may some limited, incremental effect on abuse and misuse by other means. While the reformulation is harder to crush or chew, possibly mitigating some accidental misuse, oxycodone HCl is still relatively easily extracted (b) (4)

In general, the reformulated product should be viewed as an incremental improvement over the currently available Oxycontin

Advisory Committee Meeting

A combined meeting of the ALSDAC and DSaRM Advisory Committees was held on September 24, 2009 in order to provide guidance to the Agency regarding the adequacy of the

Applicant's rigor used to assess the abuse liability of the reformulated Oxycontin, and to discuss the overall safety of the new formulation. The following questions were asked of the committee members:

1. Were the studies performed by the sponsor adequate to provide data on the abuse-deterrent characteristics of the reformulated Oxycontin product?
2. Does the change in formulation affect the overall safety profile of Oxycontin?
3. Should this application for reformulated Oxycontin be approved?

The general consensus of the Committees was that the studies performed by the Applicant were adequate to provide data regarding the physicochemical abuse deterrent characteristics of the reformulated Oxycontin, and that these characteristics provide an incremental improvement in the overall safety profile of the product. The predominant improvement of the reformulation is that it is extremely difficult to chew or crush, thereby decreasing the likelihood of a patient accidentally chewing the pill and defeating the extended-release characteristics of the formulation, a caregiver crushing the pill to administer via a G-tube, or a non-experienced abuser intentionally chewing the pill to obtain a quicker high. The Committees recognized that these situations constitute a small proportion of the methods of Oxycontin abuse or misuse, the majority being oral administration of an intact tablet, snorting, and injection. The Sponsor maintained that because it is more difficult (but not impossible) to extract oxycodone from the reformulated product (b) (4), compared to the original Oxycontin, snorting and injection may also be affected by the change in formulation. The committee was not convinced of this since although the extraction of oxycodone is more difficult than with the original Oxycontin, it is possible with (b) (4)

The Committees felt strongly that the reformulated Oxycontin should be approved only if there is a post-marketing requirement for an epidemiologic study to assess the impact of the reformulation on the abuse of Oxycontin in the community. This is the type of study that the Division and many in the pain/addiction community have viewed as very important to fully assess the impact of the new "abuse-deterrent" opioid formulations. To this end, the Sponsor will be required to submit a proposal for the design of such a study prior to approval.

Other Relevant Regulatory Issues

None

Labeling

The name of the product will continue to be Oxycontin/ oxycodone hydrochloride controlled-release tablets. Labeling changes to the current label are minimal, and include updates in the preclinical and clinical pharmacology sections. A Medication Guide has been developed to better mitigate the risks associated with Oxycontin, and will be part of the REMS described below. There will be no information in the label regarding the physicochemical attributes of the formulation or claims regarding tamper or abuse-resistance. At this writing, discussions regarding labeling are ongoing with the Applicant.

Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action and Risk Benefit Assessment

I recommend a Complete Response action for the reformulated Oxycontin because of the consensus of the Division and the members of the September 24, 2009 Advisory Committees that there be a post-marketing requirement for an epidemiologic study to assess the effect of the reformulated product on the abuse of Oxycontin as a condition of approval. The Applicant has satisfactorily responded to the deficiencies communicated in the Complete Response Action of October 3, 2008. They are planning to market all strengths as reformulated Oxycontin, and have provided sufficient data to do so. The abuse liability studies appear to have been conducted with adequate rigor. While it is clear from the results of the in vitro abuse liability studies that this formulation will not be a panacea for abuse of Oxycontin, nor is it completely abuse “resistant”, it does appear to convey an incremental improvement over the marketed Oxycontin in terms of “tamperability”. The true “abuse resistance” of this formulation can only be determined by long-term epidemiologic studies of rates of abuse in the community.

In order to mitigate the risks of abuse, misuse, overdose and addiction, a REMS will be implemented upon approval of this product. Oxycontin, as an extended-release opioid, will become part of the class-wide REMS for these products currently under development. In the meantime, an interim REMS, described below, will be put in place until required elements of the class-wide REMS have been determined. The Agency has made a determination that approvals of extended release opioids should not be delayed while the development of the class-wide REMS is in progress, as long as the safety profile of the drug is not worse than the currently marketed long-acting opioids. For these drugs, an “interim REMS” will be implemented until the class-wide REMS is finalized. The reformulated Oxycontin is expected to have the same safety profile as the currently marketed product, and therefore falls into this category.

- Recommendation for Postmarketing Risk Management Activities

As determined during the first review cycle, a Risk Mitigation and Evaluation Strategy must exist for Oxycontin to address the risks of abuse, misuse, overdose, and addiction. Since Oxycontin belongs to the class of extended-release opioid products, the REMS currently in development for these drugs must also be adopted by the Applicant. Until that occurs, the Agency has determined that an “interim REMS” must be put into place until the class-wide REMS is implemented. Once the necessary elements of the class-wide REMS are determined, the Applicant will be notified in writing and will be required to submit a modified REMS to incorporate those elements.

The request for an interim REMS, sent to the Applicant on June 17, 2009, included the following requirements:

1. Medication Guide
2. Communication Plan
 - To include educational materials for prescribers that address proper patient selection, dosing and administration, general information

regarding opioid abuse, misuse and addiction, risks of Oxycontin, and proper storage in order to keep drug away from children.

- A description of the audience for the communication plan must be included, as well as a schedule for how and when the plan's materials are to be distributed.

3. A Timetable For Submission Of Assessments

Additional details regarding the above requirements are discussed in Dr. Hertz's CDTL memo from the first review cycle.

As requested, the Applicant submitted an interim REMs that included the above elements. The Communication Plan consists of a Dear Prescriber Letter, Dear Pharmacist Letter, and a brochure entitled "Prescribing Oxycontin: A Healthcare Professional Guide".

The review of the elements of the REMS (conducted by DAARP, OSE (DRISK), DMETS, and the Office of Compliance) and discussions with the Applicant regarding the REMS are currently in their final stages.

- Recommendation for other Postmarketing Study Commitments

The Applicant is required to perform an epidemiologic study to assess the impact of the reformulation on the abuse of Oxycontin in the community. To that end, the Applicant must submit a proposal presenting the design of such a study prior to approval.

- Recommended Comments to Applicant

The following comments will be conveyed to the Applicant in the Complete Response Letter:

1. We request that you propose a study and/or clinical trial to address the following issue:

Will the changes made to the OxyContin formulation that are the subject of this application and which are intended to provide misuse and abuse-deterrence actually result in a decrease in misuse and abuse, and their consequences, addiction, overdose and death, in the community.

2. Submit your protocol proposal and a timetable according to which you are going to conduct your study.
3. You must submit an acceptable REMS and REMS Supporting Document prior to final approval of this new drug application.

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

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/s/

ELLEN W FIELDS
09/30/2009



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Avenue, Silver Spring MD 20993
Tel: (301) 796-2280

Medical Officer Review

NDA: 20-553 (Sequence 0013) and 22-272
IND: 29,038
Drug Name: OxyContin® (oxycodone hydrochloride controlled-release) tablets
Sponsor: Purdue Pharma
Type of Submission: Proposed Pediatric Study Request and report for Study (b) (4)
Date of Submission: December 18, 2008
Date of Receipt: December 23, 2008
Date of Review: April 23, 2009
Reviewer: Anjelina Pokrovnichka, M.D.
Team Leader: Robert Shibuya, M.D.
Project Manager: Lisa Basham

Background/Regulatory History:

OxyContin is a tablet that contains oxycodone, the active ingredient, in a controlled-release (CR) disintegrating matrix, designed to deliver drug with a 12-hour dosing interval. In this submission, Purdue Pharma has submitted a Proposed Pediatric Study Request (PPSR) that is, in essence, a request for an (b) (4) Pediatric Written Request (PWR) for OxyContin®.

This product has a long regulatory history (b) (4)

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

/s/

Anjelina Pokrovnichka
4/24/2009 02:08:29 PM
MEDICAL OFFICER

Robert Shibuya
4/24/2009 02:12:22 PM
MEDICAL OFFICER

I concur with Dr. Pokrovnichka's review and recommendations.



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

Summary Review for Regulatory Action

| | |
|---|--|
| Date | September 30, 2008 |
| From | Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia and Rheumatology Products |
| Subject | Division Director Summary Review |
| NDA # | 22-272 |
| Applicant Name | Purdue Pharma, L.P. |
| Date of Submission | November 29, 2007 |
| PDUFA Goal Date | May 29, 2008 |
| Proprietary Name / Established (USAN) Name | OxyContin® Oxycodone hydrochloride |
| Dosage Forms / Strength | Extended-release tablets 10 mg, 15 mg, 20 mg, 30 mg, 40 mg |
| Proposed Indication | For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time |
| Action: | Complete Response |

| Material Reviewed/Consulted | |
|------------------------------------|--|
| OND Action Package, including: | |
| Medical Officer Review | Jin Chen, M.D., Ph.D. |
| Statistical Review | N/A |
| 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 |
| DSI | Jacqueline A. O'Shaughnessy, Ph.D.; C.T. Viswanathan, Ph.D. |
| CDTL Review | Sharon H. Hertz, M.D. |
| OSE/DMEDP | N/A |
| OSE/DAEA | N/A |
| OSE/DRISK | Mary Willy, Ph.D.; Gerald Dal Pan, M.D. |
| DEPI | N/A |
| Maternal Health Team | Richardae Araojo, Pharm.D.; Karen Feibus, M.D., Lisa Mathis, M.D. |

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

DAEA=Division of Adverse Event Analysis

CDTL=Cross-Discipline Team Leader

DEPI= Division of Epidemiology

1. Introduction

Purdue Pharma, L.P. has 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 has submitted data from a number of studies to support the new formulation's capacity to resist compromise of the controlled-release features. This review will focus on the quality of this data and the potential impact of these changes on the abuse, misuse and diversion of OxyContin.

2. Background

OxyContin was originally approved in 1995. It is a modified-release formulation of oxycodone and was initially labeled as being less likely to be abused compared to other potent opioids. This assertion was based on the fact that the levels of abuse and addiction of any specific opioid are thought to be at least in part correlated with the rapidity of onset (T_{max}) and higher levels at onset (C_{max}) of the pharmacodynamic effects of the drug. However, it became clear over the ensuing five years that the OxyContin controlled-release system could be compromised with little effort and minimal expertise, thus allowing the rapid release of moderately to extremely high doses of oxycodone. (b) (4)

Even more concerning was the fact that the majority of the cases of addiction, overdose and death being reported to the AERS system and in the lay press were occurring in otherwise normal, healthy young people ingesting a compromised, or even an intact product, for a recreational “high.” Compounding this problem, Purdue had aggressively marketed OxyContin to a broad group of prescribers and the product became widely available in the community for diversion and abuse. The medical community had also recently been admonished that pain had been significantly under treated in the past. Practitioners with limited experience in pain management, under pressure to adequately treat pain under new practice recommendations and guidelines, and with a false sense of security regarding the abusability of OxyContin, began prescribing OxyContin with near abandon. This perfect storm of events led to a major public health crisis, particularly in specific regions of the U.S.

Over the past eight years, FDA and other government agencies have attempted to limit the abuse, misuse and diversion of OxyContin by a variety of mechanisms, including the addition of stronger warnings in the product label, removing wording from the label that suggested the product was less likely to be abused, educational programs directed at youthful abusers, the implementation of a multi-component risk management program (that includes physician/prescriber/patient education, as well as surveillance and intervention strategies for signals of abuse and diversion), and participation in numerous public hearings, Congressional briefings and advisory committee meetings. Unfortunately, these efforts have seemingly had little impact as, over this same period, the abuse of prescription drug products has continued to increase, and the abuse of opioid drug products has become a major public health concern across the country.

One additional effort to intervene in the abuse of prescription opioid drug products that has been recommended by the Agency, as well as by numerous other stakeholders, is the development of “abuse-resistant” formulations. FDA has encouraged the development of these formulations but has also been clear that we will not approve new indications for or labeling that is suggestive of abuse resistance for these new formulations unless an application is accompanied by data from long-term epidemiological studies that clearly demonstrate that abuse, misuse and diversion have been reduced. However, in order to provide some incentive to sponsors, above and beyond their public health responsibility, we have noted that we would

consider allowing limited data from studies that evaluated the abuse-resistant features of the products to be added to appropriate sections of the labeling. As abuse-resistant formulations generally fall into two categories, those with changes to physiochemical properties and those with changes to pharmacologic properties, this information would most likely reside in the Product Description or Clinical Pharmacology sections of the product insert.

This new formulation of OxyContin provides physiochemical features which purportedly will make it more difficult to compromise the controlled-release features of the product and which may, thereby, result in a reduction in abuse. The sponsor has submitted a number of studies meant to document this improvement to the formulation. As this is the first submission of an abuse-resistant opioid formulation, the Agency felt that it was essential that the application be discussed at a joint public meeting of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committees. The joint committee meeting was held on May 5th and the outcomes are discussed in more detail below. However, the general consensus of the committee members was that the quality of the data presented by the sponsor was wholly inadequate to support their contention that the formulation changes would provide any reduction in abuse of the product; and many of the committee members expressed concerns related to the safety of the new formulation.

One additional concern was raised with the sponsor even prior to their having submitted the application. At the pre-NDA meeting for this application, Purdue informed the Division that they had not yet successfully reformulated the two higher strength (60- and 80-mg) tablets. The Division expressed clear concern at that time that the reformulated lower-strength tablets should not be marketed at the same time as the original higher-strength tablets, due to the risk of misconceptions and the resultant medication errors that might occur. While the 60-mg tablets have not been marketed for some time, the 80-mg tablets remain on the market. This application does not include any data related to the higher-strength tablets. Purdue representatives at the recent advisory committee meeting announced that they have successfully reformulated the higher-strength tablets and that they will be submitting a supplement for those products soon. However, to date the data are pending submission.

3. CMC

This formulation of OxyContin consists of oxycodone hydrochloride in a (b) (4) of polyethylene oxide and magnesium stearate. (b) (4)

I agree with the CMC review team that there are no outstanding CMC issues for this application. However, the attributes of this new formulation that were developed to provide abuse resistance were tested by the sponsor and reviewed by the Controlled Substances Staff (CSS) and require some discussion.

From Dr. Hertz's CDTL memo, pages 3 through 5:

“As described in the reviews by Dr. Lori Love of the Controlled Substances Staff and Dr. Jin Chen, the applicant has performed a number of tests to evaluate the extent to which the new formulation can withstand the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product. (b) (4)

The details of the results of this testing are provided in a series of tables taken from the review of Dr. Chen.

“The reformulated product requires more effort to crush than the original product. The ... attempts to crush the tablets result in larger-sized particles than when the original formulation is crushed which results in a fine powder. When crushed, approximately (b) (4) of oxycodone is released from the new formulation when it is exposed to simulated gastric fluid (SGF) in contrast to the (b) (4) released from the original formulation.

“When the reformulated product undergoes crushing (b) (4) and is then exposed to a few (b) (4) of liquid, it became a viscose gel, in contrast to the original formulation which can be dissolved into solution. (b) (4)

“The results of (b) (4)

4. Nonclinical Pharmacology/Toxicology

I agree with the Pharmacology/Toxicology review team that there are no outstanding issues for this application.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor provided data documenting that the old and new formulations are bioequivalent and that the 10-mg, 15-mg, 20-mg, 30-mg and 40-mg tablets are dose proportional under fasting conditions.

Based on an inspection of the site that performed the bioequivalence study, the Division of Scientific Investigations (DSI) determined that the identity of the QC sample for two runs, used for samples from six subjects, was not adequately documented and it is unclear whether the actual concentration of the sample that was used is (b) (4) ng/mL. The CRO attributed this to documentation error and, based on their assessment, concluded that the concentration is (b) (4) ng/mL. DSI, however, concluded that the CRO's conclusion is based on indirect evidence and that there is no direct documentation that would permit identification of the actual sample and, therefore, the accuracy of the subject samples cannot be assured. In an e-mail dated May 19, 2008, Dr. Suresh Doddapaneni, Deputy Director of the Division of Clinical Pharmacology 2, stated that the sponsor could either exclude the data from the six subjects and reanalyze the bioequivalence data or reanalyze the subject samples, if there is enough left, to confirm the previous results. Therefore, before data from Study OTR1005 can be accepted, the sponsor will need to reanalyze and submit the data from study OTR1005 demonstrating bioequivalence after completely excluding data from subjects 5040, 5041, 5042, 5043, 5044, and 5045. Alternatively, they may reanalyze the plasma concentrations as identified and confirm the original values.

In his review, Dr. Chen raised concern that the in vitro oxycodone release data from the intact tablets did not correlate with the in vivo pharmacokinetic/bioequivalence data. He suggested that caution should be taken in interpreting the in vitro dissolution data for the new compared to the old formulation, and in assessing the in vitro dissolution results from the crushed (b) (4) tablets from the perspective of their ability to dose dump. However, in the same e-mail noted above, Dr. Doddapaneni explains:

There is no in vitro and in vivo correlation for the current or new formulation. I guess, [Dr. Chen's] point is that in spite of the significant in vitro release differences (for the first 45 minutes that he is comparing), the two products were bioequivalent. This is not surprising since there is no IVIVC for the product. However, within each product the dissolution data shows a consistent profile and will have set dissolution specifications. Within each product, you can still use the dissolution data for qualitative and somewhat semi quantitative purposes to assess changes in the release profile for the product before and after it is subjected to tamper. On either end of the spectrum, it will be somewhat easier to interpret the data if the product is not tamper resistant, its release profile will be like an immediate release product and if it is tamper resistant it will retain its original profile. Intermediate release profiles will be a bit harder to interpret but in light of the lack of [IVIVC] we have to interpret the data conservatively.

6. Clinical Microbiology

No clinical microbiology data were necessary for this application.

7. Clinical/Statistical-Efficacy

No new efficacy data were submitted with this application. The Division agreed with the sponsor that, if they were able to show bioequivalence between the old and new formulations, no new efficacy data would be required.

8. Safety

I agree with Drs. Chen and Hertz that the safety data collected from the pharmacokinetic studies did not raise any new concerns regarding the safety profile of the product when used properly compared to the original formulation.

9. Advisory Committee Meeting

The following questions were posed to the joint advisory committee members at the May 5th meeting:

1. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse and diversion of the product in the community. Do the available data suggest that this reformulation of OxyContin will likely reduce its abuse, misuse and diversion?
2. Currently, only the 10-mg, 20-mg, 30-mg and 40-mg strengths have been reformulated, although there are plans to reformulate the 60-mg and 80-mg strengths in the future. Could marketing and promotion of the lower, reformulated strength products as less abusable, prior to reformulation of the higher strength products, result in the misconception that the higher, non-reformulated strengths also provide a decreased risk of abuse? If so, are there ways to minimize this misconception? Given this concern, is this risk acceptable considering the potential benefit of the changes to the formulation for the lower strength products?
3. Many of the cases of addiction, overdose and death associated with OxyContin abuse have been due to ingestion of the product without manipulation of the extended-release properties. Could inclusion of data on the physicochemical attributes of the new formulation into the product labeling potentially mislead prescribers or patients into thinking that this new formulation of OxyContin is less likely to be addictive or unlikely to be abused or result in addiction or overdose? If so, is this risk acceptable considering the potential benefits of the changes to the formulation?
4. If you concluded in Question 1 that the data suggest that this reformulation of OxyContin is likely to reduce its abuse, misuse and diversion, do you recommend inclusion of any of the data into the product labeling? If so, which specific data do you think should be incorporated into the labeling?
5. If you do recommend any of these data be placed into the product label, are there risk minimization strategies that need to be put in place to support the appropriate use of this product, e.g., additional language in labeling (please specify), educational information that will describe proper use and the potential for misuse and abuse of the product, special educational requirements/training for prescribers, limitations on which patients should be treated with the product, formal agreements between prescribers and patients for proper use, registries for prescribers?

Dr. Hertz has concisely and thoroughly explicated the discussion points on which the committee members focused in response to the Division's questions. They are replicated below from pages 9 and 10 of her review:

- The testing of the properties of the new formulation was inadequate. The testing should be done in a blinded manner, using larger numbers of tablets, and should be carried out by an independent third party. Experienced abusers should be used as a resource to determine what methods are likely to be used to try and defeat the new formulation and these conditions should be used for testing.
- The data must be presented in a more scientifically sophisticated manner.
- There was much concern expressed about marketing the lower doses and keeping the original formulation 80 mg tablets on the market.
- There was concern that there could be a false sense of security that the new formulation was less abusable that could result in more prescribing of the product and so more abuse.
- There was much concern about the variability of release of oxycodone across the strengths as a result of the different methods of manipulation. This variability could result in an abuser inadvertently overdosing by not being able to accurately predict the amount of oxycodone that they can obtain from OxyContin tablets from one time to the next.
- Labeling should be very limited, many said no change, to avoid any misunderstanding of the product and to prevent false promotional claims.
- The risk minimization program should be much more comprehensive addressing enhanced education, regulation and accountability. It was particularly noted that a prospective plan for a response by the applicant must be required to address any data that indicates more abuse is detected following the marketing of the reformulation.
- The risk minimization program should be considered on a class basis, not just OxyContin.
- There should be enhanced oversight of marketing.
- In the absence of data to suggest an advantage over other opioids, and given the data presented about the amount of OxyContin abuse and possible increased liking of oxycodone compared to some opioids or comparable liking to heroin, the indication should be changed to severe pain only.
- Concern was also voiced it would be difficult to perform adequate postmarketing assessments of the effect of the change in formulation using OxyContin name and with a similar appearance to the original formulation.

I would add that some committee members did indicate that even an incremental change in the abuse potential for this product could have a potentially important impact in preventing overdoses and addiction in certain types of abusers; and that this new formulation might reduce overdoses due to improper use by health care practitioners, e.g., nurses crushing the tablet to put down an NG tube.

10. Pediatrics

Pediatric data was not submitted in this application and the application does not fall under the authority granted to FDA by PREA.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The sponsor's proposed labeling has not been fully reviewed on this cycle. The questions raised regarding the adequacy of the data submitted in the application do not allow us to make a reasonable attempt to address the changes from the original labeling that would be necessary to clearly define the quality and attributes of the new product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Risk Benefit Assessment

OxyContin and other controlled-release potent opioid drug products are essential components of the analgesic armamentarium for the treatment of chronic pain. Not only do they provide convenience to these patients by reducing the number of daily doses required, but they also provide a pharmacokinetic profile that results in reduced serum level peaks and troughs, and thereby an improvement in the consistency of effective analgesia and a potential reduction in opioid-related side effects that are often correlated with high peak serum levels. However, the abuse, misuse and diversion of these products, and OxyContin in particular, have had a profound impact on the public health. Therefore, providing even an incremental decrease in the abuse of prescription opioid products would be an important public health achievement. While it is not clear at this time whether the tools that are currently available to measure the impact of formulation changes on the abuse, misuse and diversion of prescription opioid products are adequate to provide an accurate assessment, it should not preclude us from proceeding with these efforts. It is essential that we tread cautiously as we move forward, avoiding if at all possible two equally important risks. First, by approving this application might we potentially be promoting the product in a manner that would lead to misconceptions about its abuse potential? Second, by not approving the product, or by restricting its use, might we be limiting availability of a product for patients with chronic pain that is safe and effective when it used properly?

Purdue Pharma has attempted to create physiochemical changes to the OxyContin product by manipulating the product's formulation in a manner that they claim will make the product's controlled-release characteristics more stable and less easily defeated. However, the studies that they performed to document the specific changes in the product's physiochemical attributes, and to demonstrate that the new formulation's controlled-release features cannot be easily compromised, are inadequate to support that claim. While the studies appear on face to be appropriately designed to elicit some of the required data, the study methodologies were poorly defined and the implementation of the studies lacked scientific rigor

and control for potential bias. The studies also have limitations for which the sponsor has not provided adequate rationale. (b) (4)

The studies, as performed, also demonstrate that a substantial and quite variable amount of oxycodone can still be extracted even with the new physiochemical features of this formulation. After crushing (b) (4) of the oxycodone was recovered, and a significant degree of variability was also found in the amount of oxycodone that could be extracted from different strength tablets under the same testing conditions. As Dr. Hertz commented in her review, “While the safety and efficacy of a drug product is usually primarily focused on the patient for whom it is indicated, the possibility of an increase in risk to abusers cannot be dismissed, particularly as the risk includes overdose and death or injury and has public health implications for a product so widely abused.”

Therefore, while the physiochemical changes in this new formulation of OxyContin might provide an incremental decrease in the ability of abusers to compromise the controlled-release component, the sponsor has not provided data that has been obtained in a rigorously scientific manner to support this claim and I am unable to make a thorough risk-benefit assessment in the absence of quality data. I also remain concerned that the data that was collected shows a potential for serious adverse events to occur due to the limited and poor quality documentation of the variability in the quantity of oxycodone that will be released after manipulation of the controlled-release features. Given the previous behavior exhibited by the sponsor, it is essential that they employ the highest level of scientific rigor, and document a clear absence of potential bias, before I would be able to accept their data in support of even an implicit claim of increased abuse resistance. (b) (4)

Finally, it is essential that simultaneously marketed OxyContin tablets of different strengths are all of the same formulation. The risk of having the lower-strength tablets from the new formulation available to prescribers and patients at the same time as the higher-strength tablets from the old formulation is unacceptable. Dosing errors would be essentially inevitable, with the likelihood of resultant overdoses and significant morbidity and mortality. However, if the sponsor would be willing to use a new trade name for the new formulation product, this risk would be substantially mitigated. This would also provide the ability to track the source of diverted drug product more accurately in the early post-marketing period when there would clearly be old and new formulation product available for diversion and

should be considered for approval of the new formulation product even when the entire line is available for marketing.

- Required Postmarketing Risk Evaluation and Mitigation Strategy (Refer to REMS Memo to File)

Dr. Hertz has outlined a number of other risk management conditions that she suggests the sponsor must meet before this application can be approved. Regarding her first suggestion:

- I agree that it will be necessary for the sponsor to provide a new product name for the reformulated strengths if they intend to continue to market the original formulation at any strength at the same time as they 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. I also agree that having a new trade name would be helpful in accurately tracking diversion of product in the immediate post-marketing period when there would clearly be both old and new formulation product available for diversion. However, I do not think that the latter would rise to the level of a requirement for approval should all of the new formulation strengths be approved to replace the old formulation strengths, as the time period during which both old and new product would be in the community would be minimal.

I do not agree with the following approval conditions outlined by Dr. Hertz:

- Unit of Use Packaging: Implementation of unit of use packaging for an opioid analgesic to assure delivery of medication guides would be an extremely difficult requirement to impose on the supply chain. As these products are dosed with extensive inter-patient variability, not to mention frequent changes in dosing for individual patients, the burden on a pharmacy to find adequate space to support the many different dose-units that would be required seems onerous. Nevertheless, I do remain open to further exploration of this option, and would consider asking the sponsor to explore this proposal and report back to the Division.
- Second-Line Therapy Indication and Limitation in the Indication to Severe Pain Only: Opioid analgesics, in general, and OxyContin, in particular, are widely prescribed, and most commonly prescribed by physicians without specific training in managing chronic pain or in the use of these potentially dangerous products. While this is certainly not the ideal situation and mandated training under the REMS is certainly appropriate, the paucity of adequately trained pain specialists and the extensive chronic pain population in the U.S. are the current reality that must be considered in restricting access to these products. There is, at best, minimal data at this

time that supports the hypothesis that oxycodone is more “likeable” or euphorogenic, or that it has more potential to result in addiction and abuse than the other potent opioids. While OxyContin has certainly resulted in far more cases of addiction, overdose and death than the other available potent, controlled-release opioid products, it remains unclear what factors have actually resulted in this outcome. Certainly, the aggressive and inappropriate promotion of the product by Purdue Pharma over many years played a significant role. Whether differences in the pharmacology also played a role deserves a full and careful evaluation with appropriately designed studies. However, there is currently inadequate data to support limiting OxyContin’s indication to second-line therapy. In regard to changing the indication to limit prescribing of OxyContin to severe pain only, this option has been discussed during at least two advisory committee meetings. I concur with the pain management and opioid experts on those committees that, not only would this simply result in physicians and patients changing their use of the terminology employed in the clinical setting to describe the degree of pain, but it would also restrict the use of the product in patients with moderately severe pain which has clearly been shown in well-designed clinical studies to significantly interfere with numerous activities of daily living in chronic pain patients.

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/s/

Bob Rappaport
9/30/2008 06:29:13 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review and Deputy Director Memo

| | |
|--|--|
| Date | May |
| From | Sharon Hertz, M.D. |
| Subject | Cross-Discipline Team Leader Review and Deputy Director Memo |
| NDA# | 22-272 |
| Applicant | Purdue Pharma |
| Date of Submission | November 29, 2007 |
| PDUFA Goal Date | May 29, 2008 |
| Proprietary Name / Established (USAN) names | OxyContin/ Controlled-Release Oxycodone |
| Dosage forms / Strength | Tablets 10, 15, 20, 30 and 40 mg |
| Proposed Indication(s) | For the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. |
| Recommended: | Approvable |

Introduction and Background

The subject of the current application represents a reformulation of OxyContin intended to reduce the abuse liability of the product by making the modified-release characteristics more robust. The changes to the formulation are purported to result in a tablet that is more difficult to crush or dissolve, and more resistant to the extraction of oxycodone by chemical means.

OxyContin is a modified-release formulation of oxycodone that was initially approved December 12, 1995 as 10 mg, 20 mg, and 40 mg tablets. An 80 mg tablet was approved January 6, 1997, followed by a 160 mg tablet on March 15, 2000, and 15 mg, 30 mg and 60 mg tablets on September 18, 2006. The applicant ceased distribution of the 160 mg tablet in April of 2001.

The misuse, abuse and diversion of prescription drugs has become a national problem. According to the National Survey on Drug Use and Health (NSDUH) by the Substance Abuse and Mental Health Administration (SAMHSA) the use of prescription drugs for non medical use is on the rise and prescription pain relievers are the most commonly misused prescription drug group. The hydrocodone/acetaminophen combination products, propoxyphene-containing products, and codeine-containing combination products are the most commonly selected in the NSDUH, followed by oxycodone-containing products. However, there appear to be greater consequences from the misuse of oxycodone-containing products. When normalized per 100,000 people in the population, the number of emergency department (ED) visit rates for oxycodone-containing products for non medical use is the highest relative to all other opioid analgesics except hydrocodone, based on data from the Drug Abuse Warning Network database (DAWN). However, when normalized per 10,000 prescriptions, the number

of DAWN ED visits for oxycodone-containing products far outnumber hydrocodone/acetaminophen products. This is due in part to the fact relatively larger number of prescriptions for hydrocodone/acetaminophen products, and the relatively greater potency per unit tablet available with oxycodone products. The rate is as much as three-fold greater for OxyContin and its generic equivalents which are available in 10 to 80 mg tablets compared to immediate-release oxycodone-containing products which are available with a maximum of 15 mg of oxycodone per tablet. The manner of abuse of prescription analgesics appears to be primarily by the oral route although, there is also abuse by nasal and intravenous routes. Most abuse of OxyContin occurs by the oral route, nearly 72%, compared to nasal or intravenous routes¹.

Toward the end of 2000 and into 2001, the Agency was made aware of a number of reports of misuse, abuse and addiction to OxyContin. The Agency responded to this situation in a number of ways. A full review of the available data was performed. The OxyContin package insert was rewritten to increase the emphasis and better convey the potential risks associated with misuse of OxyContin. Strong warnings, including addition of a boxed warning, were added to convey that crushing, chewing or dissolving an OxyContin tablet could result in delivery of a fatal dose of oxycodone. A statement that as a modified-release tablet, there was less potential for abuse was removed. In response to the reports of abuse, the applicant ceased marketing the 160 mg tablet, although there had not been much distribution of that strength. In addition, a risk minimization program (RMP) was crafted by the applicant. This RMP was designed to address three key risks: risk posed by abuse or diversion of OxyContin, risk posed by OxyContin in instances of improper patient selection, and risk posed by accidental pediatric exposure to OxyContin. The RMP has four main elements: labeling for professionals and patients, education of prescribers, surveillance to detect ongoing or new areas of the country where there was abuse, and specific intervention when signals were detected. Since time that the RMP was crafted and the package insert was amended, there is no data that shows any reduction in the misuse, abuse and diversion of OxyContin.

It was initially unclear what led to the rapid rise in use and misuse of OxyContin. It is now known that the applicant had pursued an aggressive marketing campaign following its launch that extended beyond the limits of the law. This likely contributed to the extensive prescribing of OxyContin by physicians and its availability in the community for misuse and diversion. In addition, physicians were detailed with information suggesting that OxyContin was less abusable or addictive than other analgesics. In July 2007, individuals in the company were found guilty of committing a felony, misleading the public by overstating the efficacy and safety of OxyContin, particularly as the safety pertains to the risk of addiction in the promotional material for OxyContin. In addition, there have been recent data describing the potential for the likeability of oxycodone by drug abusers and compared oxycodone to other drugs, including heroin. In a study by Comer, et. al., oxycodone and morphine were both found to be comparably likeable to heroin². This relatively high likeability of the oxycodone

¹ Carise D, Dugosh KL, McLellan AT, et. al. Prescription OxyContin Abuse Among Patients Entering Addiction Treatment. *Am J Psychiatry* 164: 1750-1756, 2007

² Comer SD, Sullivan MA, Whittington RA, Vosburg SK, Kowalczyk WJ. Abuse Liability of Prescription Opioids Compared to Heroin in Morphine-Maintained Heroin Abusers. *Neuropsychopharmacology*. 2008 Apr;33(5):1179-1191. Epub 2007 Jun 20.

may be another important contributing factor to the extent of abuse and misuse of OxyContin and must be kept in mind when considering the overall risk to benefit balance of this product.

Chemistry, Manufacturing and Controls

The CMC section of this application was reviewed by Dr. Craig Bertha. The formulation consists of oxycodone hydrochloride in a (b) (4) of polyethylene oxide and magnesium stearate. The tablets are formed by (b) (4)

In several amendments to the application, the applicant has submitted additional data and statistical analyses for the stability data and updated 4-hour dissolution acceptance criteria. A 24-month expiry was requested. Based on the stability data, statistical analysis and newly proposed (tightened) 4-hour dissolution acceptance criteria, a recalculation of the data provides support for an (b) (4)-month expiry for all strengths and packaging types.

Thebaine derived opioids including oxycodone have the possibility of an impurity in the drug substance that has a structural alert for genotoxicity, an (b) (4). (b) (4) the manufacturer who holds DMF (b) (4) for oxycodone, assures that the (b) (4) is kept at less than (b) (4).

The drug product is not compositionally proportional across strengths. The higher strengths have relatively less polymer than the lower strengths.

The applicant requested a waiver of the environmental assessment as estimates of oxycodone concentrations were below the 1 part per billion level. The inspections have all been found acceptable.

Attributes of the Reformulation

As described in the reviews by Dr. Lori Love of the Controlled Substances Staff and Dr. Jin Chen, the applicant has performed a number of tests to evaluate the extent to which the new formulation can withstand the effects of chemical and physical manipulation intended to defeat the modified-release characteristics of the product. These methods include (b) (4)

The details of the results of this testing are provided in a series of tables taken from the review of Dr. Chen.

The reformulated product requires more effort to crush than the original product. The result of attempts to crush the tablets result in larger-sized particles than when the original formulation is crushed which results in a fine powder. When crushed, approximately (b) (4) of oxycodone is released from the new formulation when it is exposed to simulated gastric fluid (SGF) in contrast to the (b) (4) released from the original formulation.

(b) (4)

When the reformulated product undergoes crushing (b) (4) and is then exposed to a few (b) (4) of liquid, it became a viscose gel, in contrast to the original formulation which can be dissolved into solution. (b) (4)

The results

(b) (4)

Dr. Jin Chen concluded that the data presentation by the applicant was incomplete and that the standard deviation (SD) for the results from the dissolution and extraction studies should be reported to demonstrate the variability within and across assays. Dr. Chen also concluded that a statistical analysis of the data from the in vitro studies of the new formulation would support the applicants conclusions of a difference in the dissolution and extraction between the new and old formulations. I disagree that a statistical analysis would be useful in this setting. The determination of a meaningful difference in the results of these studies is a clinical judgment of whether the differences would likely have safety implications. However, data on the variability of the study results could be informative. Dr. Chen also suggests that there was a need for in vivo testing of the bioavailability of oxycodone following chemical and physical

manipulation noting a disconnect between the in vivo and in vitro data. He describes in vivo bioequivalence for the intact tablets, but a difference the release of oxycodone following in vitro testing of the new and old formulations as noted. There is a good correlation of in vitro and in vivo testing of the potential for dose dumping of drug from modified-release opioids in the setting of different concentrations of alcohol. Although there is one example in the literature of an apparent lack of correlation with one product, it turns out that enhanced bioavailability of drug in the presence of alcohol was not due to dose dumping from the formulation, but of enhanced permeability of the gastric mucosa from the alcohol. Therefore, I disagree that additional in vivo testing is necessary of the manipulated OxyContin formulations.

It was pointed out at the May 5, 2008, advisory committee meeting that the studies were not blinded and were conducted by Purdue personnel. Recommendations were made that the studies be conducted in a blinded manner, by an independent third party, and that the methodology be validated following consultation with individuals with experience in the extraction of opioids from modified-release formulations for the purpose of misuse (see the discussion about the advisory committee meeting below).

Nonclinical Pharmacology/Toxicology

There were three new nonclinical studies submitted in support of this application. These studies were reviewed by Dr. Beth Bolan. Oxycodone is currently classified as pregnancy category B. The Segment I and Segment III studies submitted confirm that this is the appropriate pregnancy category for this drug substance. The following taken from Dr. Bolan's review, summarizes the findings:

The segment I study, Fertility and Early Embryonic Development, demonstrated that oxycodone did not affect reproductive function in male and female rats at levels that produced parental toxicity. The NOEL for male and female fertility and early embryonic development in this study is 8 mg/kg, the highest dose tested. This dose yields an exposure margin of 0.5 on a mg/m² basis when compared to a daily dose of 160 mg/day in the human. The Segment III Perinatal and Postnatal Development study demonstrated that oxycodone did not affect peri- and postnatal development in rats at doses that produced maternal toxicity with the exception of recoverable decreases in F1 body weights observed at the highest dose (6 mg/kg). No other treatment-related toxicological findings were observed in the F1 pups and no toxicologic findings were seen in the F2 pups. Comparison of the highest dose tested in rats (6 mg/kg) yields an exposure margin of 0.4 on a mg/m² basis when compared to a daily dose of 160 mg/day in the human.

Dr. Bolan has made recommendations to update the labeling accordingly.

Clinical Pharmacology/Biopharmaceutics

The applicant was not required to perform clinical efficacy or safety studies if the reformulated OxyContin was found to be bioequivalent to the original formulation. Six

pharmacokinetic (PK) studies were submitted in support of this application. Dr. Sayed Al Habet performed the primary review of these studies. One study explored the PK characteristics of three early formulations. Two studies characterized the relative bioavailability of the 10 mg new formulation tablet compared to the original formulation under fasting and fed conditions and demonstrated that the new formulation met the standards for bioequivalence, with the 90% CI for both C_{max} and AUC within the 80% to 125% limits. Another two studies demonstrated the bioequivalence of the 40 mg new formulation tablet to the original formulation under fasting and fed conditions by the same bioequivalence standards. There was little effect of food on the bioavailability of the new formulation. One study demonstrated the dose proportionality of the 10, 15, 20, 30, and 40 mg tablets of the new formulation under fasting conditions. All of these studies were conducted in healthy volunteers who received naltrexone during the study.

The metabolism of oxycodone is generally well characterized. Oxycodone is metabolized primarily via the P450 enzymes CYP3A4 and CYP 2D6. Metabolites include oxymorphone (mediated by CYP2D6), as well as noroxycodone and noroxymorphone which subsequently undergo glucuronidation. Oxycodone is approximately 45% protein bound. The oral bioavailability of oxycodone is approximately 60-87% based on the OxyContin package insert.

No novel studies were conducted to explore the effects of age, gender, renal or liver impairment. The current OxyContin package insert (PI) describes an increase in plasma concentrations of 15% in the elderly and an increase of 25% in women when adjusted for body weight. The PI also describes that in mild to severe renal impairment, peak plasma oxycodone and noroxycodone concentrations are 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. There is also an increase in mean elimination half-life for oxycodone of one hour. In mild to moderate hepatic dysfunction, the PI describes peak plasma oxycodone and noroxycodone concentrations increases of 50% and 20%, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. The mean elimination half-life for oxycodone was increased by 2.3 hours for mild to moderate hepatic impairment.

Safety and efficacy of OxyContin have not been studied in pediatric patients. The applicant has requested a deferral for the pediatric assessment for all age groups as required under the Pediatric Research Equity Act. The deferral request is based on the current application for use in adults being ready for submission and approval. The applicant has stated that they plan to provide a proposal for pediatric data assessment including a timeline to comply with PREA.

No QT studies have been performed in support of this or the original application for OxyContin. There have been no postmarketing data to suggest that there is cardiac toxicity associated with oxycodone.

There was an investigation of Study 1005 by the Division of Scientific Investigation due to the report of a number several samples with hemolyzed samples and a run with quality control issues for one run with six subjects. The former was determined to not be a problem when validation work demonstrated that hemolysis does not interfere with the analysis of

oxycodone. For the latter, it is usual to run a quality control sample along with actual samples. The company apparently failed to document the concentration in the control sample for the one run of these six subjects samples. However, there were 88 subjects total so even dropping these six subjects from the analysis, the study is expected to still be valid and the new formulation will still be able to meet bioequivalence criteria. A reanalysis will be performed and is expected to be described in an addendum by the clinical pharmacology team.

Clinical/Statistical- Efficacy

The primary clinical review of this application was performed by Dr. Jin Chen. During the development of this new formulation, the applicant and the Division agreed that clinical efficacy and safety studies would not be required if the new formulation was bioequivalent with the original formulation. This is consistent with the acceptability of bioequivalence in support of generic drug products. As the new formulation has been demonstrated to be bioequivalent to the original formulation, no studies were performed.

Safety

As with efficacy, the applicant and the Division agreed that a demonstration of bioequivalence with the original formulation would preclude the need for clinical safety studies. There were no deaths, serious adverse events or discontinuations due to adverse events.

Advisory Committee Meeting

An advisory committee (AC) meeting was held on May 5, 2008. The concerns of the Division for the committee's input are evident in the following questions that were brought to the AC:

1. Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse and diversion of the product in the community. Do the available data suggest that this reformulation of OxyContin will likely reduce its abuse, misuse and diversion?
2. Currently, only the 10-mg, 20-mg, 30-mg and 40-mg strengths have been reformulated, although there are plans to reformulate the 60-mg and 80-mg strengths in the future. Could marketing and promotion of the lower, reformulated strength products as less abusable, prior to reformulation of the higher strength products, result in the misconception that the higher, non-reformulated strengths also provide a decreased risk of abuse? If so, are there ways to minimize this misconception? Given this concern, is this risk acceptable considering the potential benefit of the changes to the formulation for the lower strength products?

3. Many of the cases of addiction, overdose and death associated with OxyContin abuse have been due to ingestion of the product without manipulation of the extended-release properties. Could inclusion of data on the physicochemical attributes of the new formulation into the product labeling potentially mislead prescribers or patients into thinking that this new formulation of OxyContin is less likely to be addictive or unlikely to be abused or result in addiction or overdose? If so, is this risk acceptable considering the potential benefits of the changes to the formulation?
4. If you concluded in Question 1 that the data suggest that this reformulation of OxyContin is likely to reduce its abuse, misuse and diversion, do you recommend inclusion of any of the data into the product labeling? If so, which specific data do you think should be incorporated into the labeling?
5. If you do recommend any of these data be placed into the product label, are there risk minimization strategies that need to be put in place to support the appropriate use of this product, e.g., additional language in labeling (please specify), educational information that will describe proper use and the potential for misuse and abuse of the product, special educational requirements/training for prescribers, limitations on which patients should be treated with the product, formal agreements between prescribers and patients for proper use, registries for prescribers?

The discussion by the members of the AC focused on several points summarized here.

- The testing of the properties of the new formulation was inadequate. The testing should be done in a blinded manner, using larger numbers of tablets, and should be carried out by an independent third party. Experienced abusers should be used as a resource to determine what methods are likely to be used to try and defeat the new formulation and these conditions should be used for testing.
- The data must be presented in a more scientifically sophisticated manner.
- There was much concern expressed about marketing the lower doses and keeping the original formulation 80 mg tablets on the market.
- There was concern that there could be a false sense of security that the new formulation was less abusable that could result in more prescribing of the product and so more abuse.
- There was much concern about the variability of release of oxycodone across the strengths as a result of the different methods of manipulation. This variability could result in an abuser inadvertently overdosing by not being able to accurately predict the amount of oxycodone that they can obtain from OxyContin tablets from one time to the next.
- Labeling should be very limited, many said no change, to avoid any misunderstanding of the product and to prevent false promotional claims.
- The risk minimization program should be much more comprehensive addressing enhanced education, regulation and accountability. It was particularly noted that a prospective plan for a response by the applicant must be required to address any data that indicates more abuse is detected following the marketing of the reformulation.
- The risk minimization program should be considered on a class basis, not just OxyContin.

- There should be enhanced oversight of marketing.
- In the absence of data to suggest an advantage over other opioids, and given the data presented about the amount of OxyContin abuse and possible increased liking of oxycodone compared to some opioids or comparable liking to heroin, the indication should be changed to severe pain only.
- Concern was also voiced it would be difficult to perform adequate postmarketing assessments of the effect of the change in formulation using OxyContin name and with a similar appearance to the original formulation.

Pediatrics

Safety and efficacy of OxyContin have not been studied in pediatric patients. The applicant has requested a deferral for the pediatric assessment for all age groups as required under the Pediatric Research Equity Act. The deferral request is based on the current application for use in adults being ready for submission and approval. The applicant has stated that they plan to provide a proposal for pediatric data assessment including a timeline to comply with PREA.

Other Relevant Regulatory Issues

NA

Labeling

The applicant proposes to substitute the new formulation for the old formulation with the same trade name and similar appearance with the indicia changed from (b) (4) to “OP”.

The applicant proposes changes to the DESCRIPTION section:

- The 10 mg, 15 mg, 20 mg, 30 mg and 40 mg tablets contain the following inactive ingredients: hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain: hydroxypropyl cellulose.

The 15 mg tablets also contain: black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain: polysorbate 80 and red iron oxide.

The 30 mg tablets also contain: polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.

- OxyContin 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg Tablets are an eroding matrix formulation of oxycodone hydrochloride where the release of the drug is controlled by the matrix. The tablets are composed of a controlled-release core with a film coat. During *in vitro* testing, (b) (4)

When in contact with aqueous media, the tablets or the fragments formed a gelatinous mass.

- The 80 mg tablet contains the following inactive ingredients: (b) (4)
FD&C blue No. 2, hydroxypropyl cellulose, (b) (4)
and yellow iron oxide.

- During *in vitro* testing, (b) (4)
When in contact with aqueous media, the tablets or the fragments formed a gelatinous mass

- The 80 mg tablets are formulated using the AcroContin® delivery system. Release of oxycodone from the AcroContin® delivery system results from dissolution of the oxycodone followed by diffusion through the tablet matrix. The water-insoluble matrix of the AcroContin delivery system renders the oxycodone release from the OxyContin® Tablets independent of surrounding pH.

The applicant updated DOSAGE FORMS AND STRENGTHS to reflect the addition of the 15 and 30 mg tablets and the change in the indicia on the 10 through 40 mg tablets.

The CLINICAL PHARMACOLOGY section has been updated to reflect the bioequivalence studies and the dose proportionality study.

The HOW SUPPLIED section was updated to reflect the new formulation.

The Division has requested the applicant create a medication guide. This will serve the purpose of providing information to patients more reliably than the current patient package insert which is not distributed. It will also form one of the elements of a new REMS to replace the existing RMP.

The proposed labeling changes are not acceptable as written. It is unlikely that there will be a clear understanding of the differences in the new and old formulations and this can lead to a misconception that all of the product is more difficult to physically manipulate. Emphasizing the resistance to manipulation may also lead to a misunderstanding of what the new physical attributes can and cannot do in the context of misuse and abuse of this product.

Recommendations/Risk Benefit Assessment

- Recommended regulatory action: Approvable
- Risk Benefit Assessment and Recommendation for Postmarketing Risk Management Activities

The applicant has developed a new formulation of modified-release oxycodone, to be marketed under the name OxyContin, that has properties to enhance the resistance of the tablet to physical and chemical manipulation intended to defeat the modified-release properties. Approximately 30% of the misuse of OxyContin is by a non-oral route, either snorting or injecting which is based on crushing the original formulation of OxyContin. Of the remaining 70% of abuse that is oral, it is not known how much might be due to chewing or crushing the tablets versus swallowing them whole. Based on the data about the difficulty crushing the new formulation to a fine powder, it seems that this product would be fairly unattractive for snorting. It is also apparently more difficult to extract the oxycodone into aqueous solution for the purpose of intravenous injection using a relatively small amount of volume. Simple crushing also does not lead to release of as large amount of oxycodone when exposed to simulated gastric fluid as the original formulation; this may represent an improvement against accidental overdose resulting from chewing by patients, and may protect some uninformed individuals who are new to the abuse of OxyContin. However, based on the methods tested, a fairly large amount of oxycodone is extractable by crushing and subsequent exposure to a variety of solvents, with the range of (b) (4) of the oxycodone obtainable. It is also known that fairly sophisticated chemical extraction methods can be applied to prescription drugs by highly motivated individuals. There is a fair degree of variability in the amount of oxycodone obtainable from different strengths under the same conditions of extraction, which may be dangerous in the setting of attempts to abuse the product. The variability demonstrated in the testing provided may result in the inability to predict the amount of oxycodone that can be obtained from a manipulation applied to the new formulation and thereby a dose may be selected that will result in an overdose. While the safety and efficacy of a drug product is usually primarily focused on the patient for whom it is indicated, the possibility of an increase in risk to abusers cannot be dismissed, particularly as the risk includes overdose and death or injury and has public health implications for a product so widely abused.

However, it cannot be dismissed that this new formulation does offer some modest safety enhancements to a limited number of individuals, both legitimate patients and intentional misusers. As described during the AC by Dr. Kristina Arnwine of the Division of Medication Error Prevention in the Office of Surveillance and Epidemiology, the most common reports of manipulation found in the AERS database were crushing followed by chewing. A small number of these cases involved medication errors in which healthcare professions manipulated the tablets for ease of administration, such as crushing to administer down a gastric tube. The remainder appeared to be manipulation for the intent of abuse. The incremental improvement in the resistance of the product to chewing and crushing by patients or abusers may result in fewer serious overdoses and deaths.

It is however, very important to understand whether the results of the testing provided by the applicant are robust and reliable, particularly for the first product to be marketed with physical

properties specifically intended to protect the modified-release characteristics. As discussed during the AC, it is not clear that the testing of the product has been adequate to date. In addition to a more robust set of tests, it is important to understand the effects of all manipulations on all strengths given that the product is not compositionally proportional. Furthermore, it is important that the testing be done in a setting of adequate impartiality through blinding and use of a third party.

While the problem of OxyContin abuse, misuse and diversion has been known for several years, recent data reviewed and presented at the advisory committee describe an alarming picture of misuse to a large extent due to the availability of OxyContin in the community. According to the NSDUH by SAMHSA, the primary source for prescription drugs that are abused is the medicine cabinet, so it follows that the amount of product available in the community plays a large role in access by abusers. This is compounded by data suggesting that oxycodone has a very high degree of likeability by abusers with effects similar to heroin.

At this time, I think it is premature to approve this application, however I believe that ultimately, even the small incremental improvement this reformulation represents is at least a first step in the right direction for improving the safety of modified-release opioids. In order to have an overall favorable risk to benefit balance, additional data is needed and several conditions must be met:

1. All dosage strengths must be ready for marketing at the same time.
2. The new formulation must be subjected to new studies consisting of blinded testing for the evaluation of the effects of physical and/or chemical manipulation, preferably by an independent third party.
3. The methods used to assess the physical characteristics of the product must be reassessed. Individuals experienced in the intentional extraction of oxycodone from OxyContin with the intent of misuse should be consulted for the purposes of determining the best methods for testing that will most likely be 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.
4. Based on the lack of comparative data to suggest that OxyContin offers a benefit to patients beyond that from other available modified-release opioids, and in the presence of data that suggests oxycodone is a target of greater abuse and has a greater abuse potential compared to some of the other modified-release opioids, it is appropriate to change the indication from moderate to severe pain requiring around-the-clock opioids for more than a few days to severe pain in patients requiring around-the-clock opioids for more than a few days. This could result in a reduction in the number of prescriptions of OxyContin and thus the amount of OxyContin in the community. This must be done very carefully so as to avoid the unintended consequence of other modified-release of opioids becoming substitutes for OxyContin in the abuse statistics.

5. A Risk Mitigation and Evaluation Strategy (REMS) must be created with the following elements:
 - a. A medication guide in place of the patient package insert. There are few patient package inserts that are ever distributed. Medication guides are required to be distributed with each prescription dispensed.
 - b. A method of delivery for the medication guide. Although required by law, medication guides are often not received by patients. One option that has been helpful with other products has been to attach the medication guide to unit of use packaging. This is a challenging concept for a chronically administered analgesic with a very wide dosing range, but unit packages with different counts could be made available, for example, 30, 90, and 180 count bottles.
 - c. Educational program for physicians that includes information on
 1. the risks and benefits of the use of OxyContin for the management of chronic non-cancer pain and chronic cancer pain in non-terminal patients
 2. the risks and benefits of chronic opioid use
 3. how to assess patients for risk factors that may predispose them to abuse or misuse
 4. how to appropriately manage patients over a long-term period including patient contracts, intermittent urine toxicology screenings, use of a single pharmacy
 - d. Physician attestation of knowledge of the risks and benefits of chronic opioid therapy and the education materials noted above.
6. The applicant commit to contract to have an independent review conducted of the postmarketing surveillance study proposed to monitor the impact of the new formulation on the safety of OxyContin.
7. A prespecified decision tree and intervention action plan to address any findings of an increase in misuse, abuse or diversion of OxyContin following marketing of a new formulation.
8. An additional consideration is making OxyContin “second line” therapy. This would result in patients not being given OxyContin as their first opioid, or even the first modified-release opioid. This would result in a fewer number of OxyContin prescriptions being given to patients, but as with the previous recommendation, care would need to be taken that the result is not simply substituting another product for OxyContin in the abuse statistics. This would be second line therapy based solely on safety considerations, as there is no data to suggest that OxyContin is effective when other opioids are not.
9. Serious consideration should also be given to using an new tradename for the reformulated product. 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.

- Recommendation for other Postmarketing Study Commitments

The applicant will need to conduct appropriate pharmacokinetic and adequate and well-controlled efficacy and safety studies in pediatric patients.

An adequately designed postmarketing study will be required that is capable of analyzing the trends in abuse, misuse and diversion of the new formulation OxyContin and provide a comparison to the trends that have been seen with the original formulation. The results of this study will be used to determine the efficacy of the REMS put into place at the time of approval. The protocol for this study is to be reviewed by an independent party with expertise in risk management, study design and controlled substances. This study can only be conducted postmarketing as it will assess the impact of the formulation change and the new REMS once the product is on the market.

- Recommended Comments to Applicant

Items 1 through 9 above and the postmarketing requirements are to be conveyed to the applicant.

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/s/

Sharon Hertz
5/13/2008 05:49:49 PM
MEDICAL OFFICER



Clinical Review

NDA[★]

Division of Anesthesia, Analgesia, and Rheumatology Products
Center for Drug Evaluation and Research • Food and Drug Administration
Silver Spring • Maryland

| | |
|----------------------------|---|
| NDA | 22-272* |
| DRUG NAME | OxyContin Tablets 10, 15, 20, 30 and 40 mg (Reformulation) |
| PROPOSED INDICATION | Moderate to severe chronic pain |
| APPLICANT | Purdue Pharma Inc. |
| LETTER DATE | Nov 29, 2007 |
| STAMP DATE | Nov 29, 2007 |
| PDUFA DATE | May 29, 2008 |
| REVIEW COMPLETE | May 12, 2008 |
| MEDICAL OFFICER | Jin Chen, MD, PhD |
| MEDICAL TEAM LEADER | Sharon Hertz, MD |
| PROJECT MANAGER | Lisa Basham, MS |

* This is an initial NDA submission without clinical efficacy and safety studies and the *Clinical Review Template* is not followed for this review.

BACKGROUND

In this NDA, the applicant has reformulated their currently-marketed oxycodone extended-release (ER) tablets, OxyContin (NDA 20-553), to make the tablets more resistant to physical and chemical manipulation. The applicant refers this as “tamper resistant”, or *oxycodone hydrochloride tamper-resistant* (OTR) tablets, and intends for this ultimately to reduce the abuse liability of the product. As this NDA submission does not include clinical efficacy and safety studies, the Clinical Review Template was not used for this review.

The applicant intends to seek the same trade name (OxyContin), dosing regimen and indication as their currently-marketed product. The new formulation, once approved, will replace the marketed OxyContin tablets on the US market.

The applicant submitted only CMC data and the results of pharmacokinetic (PK) studies to support four dosage strengths of the OTR formulation tablets: 10 mg, 15 mg, 20 mg, 30 mg and 40 mg. The reformulation of the remaining two dosage strengths, 60 mg and 80 mg tablets, has not been completed.

There are no efficacy and safety studies submitted in this NDA. Efficacy and safety evidence of the new formulation is based on reference to the applicant’s NDA 20-553 (OxyContin tablets). This NDA is a 505(b)(1) application.

REGULATORY HISTORY

The applicant’s currently-marketed OxyContin tablets (NDA 20-553) were formulated with the AcroContin delivery system (no inherent resistance to crushing, as per the applicant) and was approved by FDA at different times for various dosage strengths, as follows:

Dosage strengths (approval dates based on the *Orange Book* online as of April 4, 2008):

- December 12, 1995: 10 mg, 20 mg and 40 mg tablets
- January 6, 1997: 80 mg tablets
- March 15, 2000: 160 mg tablets (discontinued in April 2001)
- September 18, 2006: 15 mg, 30 mg and 60 mg tablets

Currently, the following dosage strengths of OxyContin are marketed in the US: **OxyContin Tablets 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, and 80 mg.**

The indication sought for the new formulation is the same as for the currently marketed product: “*Management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time*”. The dosing regimen is also the same, one tablet every 12 hours.

A pre-NDA meeting was held on July 9, 2007. The following guidance was provided to the applicant regarding clinical development of the OTR formulation:

- Review of the data from extraction studies on the new formulated 40 mg tablets did not provide convincing evidence that this reformulation is meaningfully different from the current product.
- Extraction studies should be conducted on the new formulated 60 mg and 80 mg tablets as were performed with the 40 mg tablets.
- If a new NDA is submitted, the applicant will be required to pay a half user fee, will be required to satisfy PREA and the physician labeling rule. The NDA will be classified as a priority review (6 months).
- The language for the abuse liability (resistant to physical and chemical manipulation) in the labeling will be determined following review of the data. However, it will be excluded from the labeling until all strengths are approved (or if NDA is submitted without the 60 mg and 80 mg strengths, the tamper-resistant language can not be used in the labeling).
- If only lower strengths are submitted in the NDA, only language associated with the basic description of the new formulation would be allowed.
- If the applicant planned to discontinue the 60 mg and 80 mg strengths of the old formulation from market until they are reformulated, they will need to convince the Agency that the higher strengths are not medically necessary and their absence from the market will not create a hardship for patients.
- If all strengths are submitted with the NDA and PK/bioequivalence (BE) between the two new and old formulations is established, the same name, OxyContin, will be acceptable.
- A deferral for pediatric studies is acceptable.
- No ISS or ISE would be required if there were no relevant adverse events (AEs) reported.

CHEMISTRY, MANUFACTURING AND CONTROL STUDIES

In addition to the basic Chemistry, Manufacturing and Control (CMC) data submitted in this NDA, the applicant developed a special protocol to assess the tamper-resistance of the reformulated OxyContin tablets and submitted the [Tamper Evaluation Report](#) (Section 3.2.2 of NDA). The report included all dosage strengths (10 mg to 80 mg) of reformulated OxyContin. However, the PK data for 60 mg and 80 mg strengths were not available for this review cycle. The focus of the CMC review was on the 10 mg to 40 mg strengths; see the two CMC reviews (Jan-25-08 and April-04-08 in DFS) conducted by Dr. Craig Bertha for details.

As concluded in the CMC reviews, there are no outstanding CMC issues in the NDA submission (November 29, 2007) and amendments (up to March 25, 2008); the reformulated OxyContin tablets showed more resistance to physical and chemical manipulations than the currently-marketed OxyContin formulation. The recommendation from the CMC review team is **approval** for the reformulated strengths 10, 15, 20, 30 and 40 mg tablets.

Comparisons between new and old formulations: The new formulation (OTR) tablets 10, 15, 20, 30 and 40 mg are composed of a controlled-release core (b) (4) with a cosmetic coat. The total amount of core components is identical (150 mg) for all strengths but the (b) (4). The core matrix contributes both the extended-release and tamper-resistant properties of the OTR tablets.

The currently-marketed OxyContin tablets are formulated with the following excipients (b) (4) from the tablets: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin (from the current labeling of OxyContin, version Sep-07-2007). The tablets of this formulation have no tamper-resistant properties as the applicant stated in this NDA.

Tamper Resistance Evaluation: The resistance to physical and chemical manipulation of reformulated OxyContin (OTR tablets) was evaluated at dosage strengths of 10, 15, 20, 30 and 40 mg and compared to that of the same dosage strength of the current OxyContin products. The resistance was evaluated at the following three levels of tablet manipulation, as summarized in Tables 1 & 2 (extracted from the CMC review and the applicant's Tamper Evaluation Protocol and Report):

(b) (4)

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In addition, the applicant conducted an *in vitro* study to assess the effect of alcohol on the OTR formulation to see if there was dose dumping as a result of exposure to alcohol. The study was conducted with simulated gastric fluid without enzyme (SGF) containing 0, 4, 40 and 40% ethanol for 12 hours.

Table 8. Overview of PK studies in Healthy Subjects

(From the applicant's Table 1 in [Summary of Biopharmaceutic Studies](#))

| Study Type | Study Identifier | Objective | Study Design | Test Product and Dosing | Subject* | Duration of Treatment |
|------------|------------------|---|---|-------------------------|----------|-----------------------|
| BA | OTR1001 | Pilot, PK, Relative BA | Randomized Cross-over (fed/fasting) with naltrexone | 10 mg OTR (pilot PK) | 34 (34) | Single oral dose |
| BE | OTR1002 | Comparison of new formulation to marketed formulation | Randomized Cross-over (fed) with naltrexone | 10 mg OTR vs. OxyContin | 84 (82) | Single oral dose |
| BE | OTR1003 | Comparison of new formulation to marketed formulation | Randomized Cross-over (fasting) with naltrexone | 10 mg OTR vs. OxyContin | 84 (83) | Single oral dose |
| BE | OTR1004 | Comparison of new formulation to marketed formulation | Randomized Cross-over (fed) with naltrexone | 40 mg OTR vs. OxyContin | 84 (74) | Single oral dose |
| BE | OTR1005 | Comparison of new formulation to marketed formulation | Randomized Cross-over (fasting) with naltrexone | 40 mg OTR vs. OxyContin | 84 (80) | Single oral dose |
| PK/BA | OTR1006 | Dose proportionality | Randomized Cross-over (fasting) with naltrexone | 10-40 mg OTR | 54 (52) | Single oral dose |

OTR: oxycodone tamper-resistant (OTR) tablets; * Numbers of subjects in the parenthesis were completers.

The following conclusions are extracted from the PK review performed by Dr. Sayed Al Habet (see the PK review for details):

- OTR tablets 10 mg and 40 mg are bioequivalent to the reference drug, the marketed formulation OxyContin tablets, at the same dose strengths under fed and fasted states (Table 9).
- OTR tablets are dose proportional in both C_{max} and AUC at fasted state from 10 mg to 40 mg (Table 10).
- Ethanol from 4-40% in SGF does not increase oxycodone release for the 10 mg tablets and the 40 mg tablets, suggesting that the new formulation is less likely to result in dose dumping *in vivo*.

- The Clinical Pharmacology reviewer concluded that this NDA is acceptable provided that agreement regarding the labeling language can be reached between the Agency and the applicant.

Table 9. Bioequivalence between the new and old formulation

(From the Dr. Habet's PK review, page 97)

| Study | Dose | Condition | Cmax | | AUCt | |
|---------|-------|-----------|---------------|------------------|---------------|-----------------|
| | | | LS Mean Ratio | 90% CI | LS Mean Ratio | 90% CI |
| OTR1002 | 10 mg | Fed | 105.0 | [101.06, 108.51] | 95.7 | [93.85, 97.68] |
| OTR1003 | 10 mg | Fasted | 102.0 | [99.35, 105.42] | 98.3 | [95.20, 101.48] |
| OTR1004 | 40 mg | Fed | 99.9 | [95.40, 104.52] | 92.6 | [90.13, 95.13] |
| OTR1005 | 40 mg | Fasted | 96.6 | [92.80, 100.56] | 95.5 | [92.93, 98.18] |

Table 10. Dose-proportionality of new formulation OTR tablets 10-40 mg in fasted state

(From the Dr. Habet's PK review, page 90)

| PK Metric | Units | | 10 mg | 15 mg | 20 mg | 30 mg | 40 mg |
|------------------------------------|------------|------|------------|------------|------------|------------|------------|
| | | | OTR Tablet | OTR Tablet | OTR Tablet | OTR Tablet | OTR Tablet |
| AUC _t | (ng*hr/mL) | Mean | 135 | 194 | 247 | 375 | 495 |
| | | SD | 37.1 | 54.3 | 60.4 | 90.9 | 132 |
| | | N | 44 | 44 | 45 | 42 | 47 |
| DN AUC _t ^a | (ng*hr/mL) | Mean | 135 | 129 | 123 | 125 | 124 |
| | | SD | 37.1 | 36.2 | 30.2 | 30.3 | 33.0 |
| | | N | 44 | 44 | 45 | 42 | 47 |
| AUC _{inf} | (ng*hr/mL) | Mean | 136 | 196 | 248 | 377 | 497 |
| | | SD | 37.3 | 54.9 | 61.1 | 91.2 | 133 |
| | | N | 44 | 44 | 45 | 42 | 47 |
| DN AUC _{inf} ^a | (ng*hr/mL) | Mean | 136 | 130 | 124 | 126 | 124 |
| | | SD | 37.3 | 36.6 | 30.5 | 30.4 | 33.1 |
| | | N | 44 | 44 | 45 | 42 | 47 |
| C _{max} | (ng/mL) | Mean | 11.5 | 16.8 | 22.7 | 34.6 | 47.4 |
| | | SD | 3.06 | 4.91 | 5.73 | 7.43 | 14.0 |
| | | N | 44 | 44 | 45 | 42 | 47 |
| DN C _{max} ^a | (ng/mL) | Mean | 11.5 | 11.2 | 11.4 | 11.5 | 11.9 |
| | | SD | 3.06 | 3.27 | 2.87 | 2.48 | 3.50 |
| | | N | 44 | 44 | 45 | 42 | 47 |

Source: Tables 14.2.2-1a and 14.2.2-2a.

^a DN indicates a dose-normalized metric, where the metric has been normalized to a dose of 10 mg where applicable.

EFFICACY and SAFETY

No efficacy or safety studies with the new formulation OTR tablets were conducted. The evidence of efficacy and safety is based on bioequivalence to the currently-marketed OxyContin and the Agency's prior finding of efficacy and safety for OxyContin.

Safety database:

The applicant submitted a brief [Summary of Clinical Safety](#) in the NDA, which was primarily based on the six PK studies conducted in healthy adult subjects. A total of 405 healthy subjects (opioid naive) were treated with a single dose of the OTR tablets; 353 subjects received OTR tablets 10 mg or 40 mg and crossed over to OxyContin 10 mg or 40 mg and 52 subjects in the dose-proportionality study were exposed to a single dose of each of the OTR tablets, 10, 15, 20, 30 and 40 mg, through 4-way crossover design. All subjects received naltrexone 25-50 mg at -12, 0, 12, 24 and 36 hours relative to the OTR or OxyContin administration to minimize opioid-related AEs. Safety assessments included vital signs, physical examination, ECG, pulse oximetry, clinical lab and AE monitoring. There were no deaths and SAEs, and no new safety signals reported from these studies. As the subjects all received naltrexone, the safety database does not reflect the effects of the OTR and will not be reviewed further.

Post-marketing safety data:

There is no foreign postmarketing experience with the new formulation OTR tablets. The applicant referenced the bi-annual Periodic Safety Update Report (PSUR) submitted to NDA 20-553 on June 8, 2007.

LABELING AND MEDICATION GUIDE

Proposed Package Insert:

The proposed PI was prepared according to the new physician labeling rule (PLR), and including a patient package insert. The majority of information was taken from the current labeling of OxyContin (NDA 20-553) with minor editorial changes (see the separate labeling review from the review team).

- The proposed PI includes dosage strengths of the OTR tablets 10mg, 15mg, 20mg, 30mg and 40 mg, and the old formulation tablets 80 mg.
- The tamper-resistance properties of the new formulation are stated under DESCRIPTION, as quoted below, which primarily reflects the results from the Applicant's studies of the effects of crushing (b) (4) dissolution and extraction as reported in the [Tamper Evaluation Report](#).

During *in vitro* testing, (b) (4)

When in contact with aqueous media, the tablets or the fragments formed a gelatinous mass.

- Description of the strength 80 mg tablets is taken from the current OxyContin labeling; however, the term "AcroContin" delivery system was added into the

DESCRIPTION section. Excipients related to the delivery system but not a proprietary term such as “AcroContin” should be used.

(b) (4)

- Warnings about the risk of dose dumping due to crushing and chewing or snorting and injecting crushed tablets are present in the proposed labeling.

(b) (4)

Medication Guide (MedGuide):

Under *FDAAA Title IX, subtitle A* (effective on March 25, 2008), a REMS (Risk Evaluation and Mitigation Strategy) is required for this product to ensure that the benefits outweigh the risks. This product meets the requirements of REMS because special certification is needed for prescription and dispense and patients need certain monitoring and enrolling in a registry². One of REMS elements is to develop a MedGuide. As per the Division’s request, the applicant converted the patient package insert (PPI) originally submitted in the proposed labeling to a MedGuide. However, both format and content of the MedGuide need substantially revising. The applicant will be referred to *21CFR208* for development of an adequate MedGuide³.

SUMMARY and DISCUSSION

Therapeutic Equivalence and basic CMC:

The new formulation OTR tablets are bioequivalent to the currently-marketed OxyContin tablets at strengths 10 mg and 40 mg, and the PK profile of OTR tablets is dose-proportional from 10 mg, 15 mg, 20 mg, 30 mg to 40 mg. And there are no outstanding CMC issues with the new formulation, as per the CMC review team. The results suggest that the new formulation tablets at the strengths 10, 15, 20, 30 and 40 mg can be labeled as the marketed OxyContin tablets.

² “Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007”. *Federal Register* 03-27-2008 ([Notices](#))

³ “Medication Guide for Prescription Drug Products” *21CFR 208*

Physicochemical evaluation of tamper resistance:

The applicant's evaluation of the data from studies intended to demonstrate the resistance of the new formulation to crushing, (b) (4) and chemical extraction demonstrated that less oxycodone was extractable than the currently-marketed OxyContin tablets. These results suggest that the new formulation may be more difficult to manipulate for non-medical use (insufflation and IV injection) and may have less dose-dumping potential for oral abuse/misuse as compared with the marketed OxyContin tablets.

However, the new formulation tablets are still crushable (b) (4) and oxycodone from the crushed (b) (4) tablets is significantly extractable by (b) (4). Thus, the new formulation may not significantly reduce non-medical use (IV preparation and insufflations) of the extended-release oxycodone.

Further more, the data presentation and analysis in the **Tamper Evaluation Report** are inadequate, which makes the applicant's tamper evaluation questionable. The applicant did not specify how the data from the dissolution and extraction studies were processed and analyzed in the study report or in the study protocol. The standard deviation for oxycodone release data in the dissolution and extraction studies would be informative to demonstrate the variability within and across assays. And the *in vitro* tamper-resistant properties of the new formulation would be more convincing with a statistical analysis of the differences in dissolution and extraction between the new and old formulations.

In Vitro-In Vivo Miscorrelation:

The *in vitro* oxycodone release from intact tablets was not correlated with the *in vivo* PK/bioequivalence profile between the new and old formulations. As shown in Table 11, there was approximately (b) (4) equivalence in terms of oxycodone release *in vitro* and almost (b) (4) bioequivalence *in vivo* between the new and old formulation tablets (10 mg and 40 mg). The miscorrelation between the *in vitro* and *in vivo* results suggests that a great caution should be taken to interpret the *in vitro* dissolution data for the new formulation as compared to the old formulation and the *in vitro* dissolution results from crushed (b) (4) tablets are not reliable for assessment of oral abuse/misuse (thus dose-dumping) of this product.

Table 11. Miscorrelation between *In Vitro* Dissolution and PK/BE Profile of Intact Tablets of New and Old Formulations

(Extracted from the above Tables 3 and 9)

(b) (4)

In the *in vitro* dissolution testing, oxycodone release from the crushed (b) (4) tablets of the new formulation was (b) (4) in the simulated gastric fluids, which was about (b) (4) less than the old formulation (based on the applicant's report, Table 3). The applicant concluded that the crushed (b) (4) tablets of new formulation "retained some of controlled-release characteristics" and "therefore dose dumping is not observed" with oral chewing tablets. The applicant's conclusion is not supported by sufficient evidence:

1. The applicant's presentation of the *in vitro* data is problematic (see above). The *in vitro* controlled-release characteristics of the crushed (b) (4) tablets that the applicant concluded need to be adequately retested and verified.
2. Even the *in vitro* dissolution results are verifiable, the *in vitro-in vivo* miscorrelation of dissolution resulted from intact tablets (Table 11) suggests that the *in vivo* oxycodone release from the crushed (b) (4) tablets is unlikely to have a similar profile as in the *in vitro*, i.e., the new formulation tablets would likely have the same physical dose-dumping potential as the old formulation if chewed or taken after crushing or snorted the crushed (b) (4) tablets. Therefore, appropriate comparative PK studies with crushed (b) (4) or chewed tablets are necessary to assess the potential physical and chemical dose-dumping (with or without alcohol and other common drinks). The dose-dumping should also be assessed with snorting the crushed (b) (4) tablets.
3. Even the *in vitro* physical and chemical testing results can be adequately verified, the improvement of the new formulation in tamper-resistance might make intravenous or snorting abuse/misuse more difficult at a certain degree. However, more than 70% of abuse/misuse of oxycodone ER tablets is by oral ingestion (estimated by the applicant in the NDA submission as well as presented by SAMHSA⁴ in the recent advisory committee meeting). Dose-dumping risk associated with the oral abuse/misuse (chewing tablets and ingesting the crushed tablets) and snorting abuse/misuse can not just simply assessed with an *in vitro* testing system, even if the *in vitro* system is flawless.

Proposed Labeling:

In the proposed labeling, the applicant claims that crushed OTR tablets (b) (4) under DESCRIPTION. Although the claim is apparently supported by the applicant *in vitro* studies (dissolution and extraction), it is uncertain if the (b) (4) "will be retained *in vivo* (in terms of dose dumping) after tablets are chewed or crushed before ingestion.

Even if the applicant can demonstrate adequate *in vitro* and *in vivo* data with favorable tamper resistant properties of the new formulation over the old formulation, any (b) (4) should not be included in the labeling because any this claim would potentially promote use of the new formulation and in turn increase abuse/misuse potential, as this also concerned the joint advisory committees of May 5, 2008.

⁴ Presentation by the Substance Abuse and Mental Health Service Administration (SAMHSA) at the joint meeting of the Anesthetic & Life Support Drugs Advisory Committee and the Drug Safety & Risk Management Advisory Committee on May 5, 2008.

A tamper-resistance formulation of oxycodone ER tablets should be developed with adequate *in vitro* and *in vivo* testing and should substitute the currently-market tablets without any new labeling claim (related to abuse/misuse).

CONCLUSION and RECOMMENDATION

This NDA is recommended for ***approvable*** because of the following facts:

The bioequivalence of the new formulation at strengths 10 mg, 15 mg, 20 mg, 30 mg and 40 mg has been adequately established as compared with the currently-marketed OxyContin Tablets (NDA 20-553), and there are no outstanding CMC issues on the new formulation tablets.

The new formulation appears less dissolvable and extractable *in vitro* (in terms of oxycodone release) in commonly available solvents (b) (4) after tablet crushing (b) (4) than the old formulation, which might make parenteral abuse/misuse relatively harder. However, the applicant's *in vitro* tamper-resistance evaluation was inadequate in test design and data process/analysis.

In addition, there were no *in vivo* studies of chewing tablets, ingesting or snorting crushed tablets on potential dose-dumping, which impacts more than 70% of abuse/misuse of oxycodone ER tablets.

Without strong *in vitro* and *in vivo* evidence to prove the tamper-resistant property, the new formulation of OxyContin, even marketed without any tamper-resistance labeling claim, may increase not only potential of the non-medical abuse/misuse but also the risk of medical misuse (e.g. chewing or broken tablets).

The applicant also needs to adequately address all issues related to the proposed labeling and MedGuide (see labeling reviews from the review team for details), and must not make any claim related to (b) (4) in the labeling.

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/s/

Jin Chen
5/16/2008 10:08:42 AM
MEDICAL OFFICER

Sharon Hertz
6/2/2008 06:26:06 PM
MEDICAL OFFICER

I concur with the recommendation for an approveable action.
See my memo for differences in the overall
assessment.