

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-272

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 18, 2010

To: Bob Rappaport, MD, Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Mary Willy, MPH, Deputy Director
Division of Risk Management (DRISK)

From: Gita A. Toyserkani, Pharm.D., MBA, Senior Drug Risk
Management Analyst, Acting TL
Mary Dempsey BS, Coordinator for Risk Management
Programs, DRISK

Subject: Prior Approval REMS Modification

Drug Name(s): OxyContin Tablets
(oxycodone hydrochloride controlled-release)

Application Type: NDA 022272

Applicant/sponsor: Purdue Pharma L.P.

OSE RCM #: 2010-1354

1 Background

The Division of Anesthesia and Analgesia Products (DAAP) requested that the Division of Risk Management (DRISK) review the OxyContin (oxycodone hydrochloride controlled-release) tablets Prior Approval REMS Modification Supplement for New Drug Application (NDA 022272) submitted by Purdue Pharma L.P. on June 10, 2010. This supplemental new drug application provides for revisions to the Training Guide for Healthcare Providers, boxed warning, table of contents, references, removal of website reference, and upper/lower case text.

The OxyContin (oxycodone hydrochloride controlled-release) tablets REMS was approved April 5, 2010 with the following elements:

- Medication Guide
- Elements to Assure Safe Use
 - Healthcare provider training
 - Dear Healthcare Professional letter mailed at least three (3) weeks prior to first availability of Oxycontin
 - Prescriber re-training every two (2) years
- Timetable for Submission of Assessment

2 Material Reviewed

- April 2, 2010 Purdue submitted REMS Supporting Document
- April 5, 2010 Oxycontin REMS approval
- June 10, 2010 Purdue submitted Prior Approval REMS Modification

3 Proposed REMS Elements

The Oxycontin June 10, 2010 submission provides the proposed REMS modification, Medication Guide, Dear Healthcare Professional Letter, Healthcare Provider Training Guide, and Education Confirmation Form. The REMS Supporting Document is not included in this submission. The product is in pre-launch development and not currently marketed; therefore, it is reasonable to state that insufficient time has passed since the REMS approval to provide a meaningful assessment. The cover letter of the June 10, 2010 submission states the following:

“The approved REMS Supporting Document remains unchanged and is identical to the version submitted on April 2, 2010

Herein we are submitting the revised REMS...which include revisions only to the Training Guide for Healthcare Providers. In our view, these revisions are minor and do not change the content, but rather improve the document quality. For ease of review, the revisions are outlined below:

- “(oxycontin hydrochloride controlled release) added to headline page and the indication pg 4
- Boxed warning from approved FPI replaced current version that was developed for use in HCP Guide. This ensures that a consistent official black box warning is used in the FPI and Training Guide [this is the only one that should be in circulation]
- “Full Prescribing “ and Boxed Warning- Uppercased throughout the document

- Table of Contents (TOC moved to page 3 after black boxed warning, This ensures that the TOC precedes the Introduction section, rather than after the Introduction where it is currently located
- Removed reference to website on page 11 as not relevant to section
- References reordered to be in numerical sequence (previously jumped from #1 to # 7).”

4 Discussion and Conclusion

DRISK performed a comparison of the June 10, 2010 submitted proposed REMS and Medication Guide to the approved Oxycontin REMS and Medication Guide and found them to be identical. The revisions to the Healthcare Provider Training Guide proposed by Purdue are acceptable.

5. Recommendation

Approve the REMS modification as submitted June 10, 2010.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22272	SUPPL-5	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/

MARY J DEMPSEY
06/18/2010

MARY E WILLY
06/19/2010
I concur



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 2, 2010

To: Bob Rappaport, MD, Director
Division of Anesthesia and Analgesia Products (DAAP)

Thru: Claudia Karwoski, Pharm.D., Director
Division of Risk Management (DRISK)

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**Office of Compliance Division of Risk Management and
Surveillance**
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Subject: Review of Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): OxyContin[®] (oxycodone hydrochloride controlled-release)

Application
Type/Number: NDA 22-272

Applicant/sponsor: Purdue Pharma Inc

OSE RCM #: RCM: 2009-788

EXECUTIVE SUMMARY

OxyContin[®] (oxycodone hydrochloride controlled-release) is an opioid analgesic with the proposed indication for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesia is needed for an extended period of time. The Sponsor submitted a proposed Risk Minimization Action Plan (RiskMAP) on November 29, 2007, during the first review cycle. In accordance with section 505-1 of the FDCA, the Agency determined that a REMS is necessary for OxyContin[®] to ensure that the benefits of the drug outweigh the risks of abuse, misuse, and overdose. The Sponsor was officially notified of this requirement on June 17, 2009.

The Agency has been considering REMS elements that should be implemented for a number of opioid products, including modified-release opioids, to address the risks of abuse, misuse, and overdose. A class REMS for long-acting and high potency opioids is also being considered. Until the Agency has determined the elements or possibly a class-wide REMS, DAAP with input from OSE, has decided that an interim REMS for long-acting and high potency opioids will be required as these products are approved.

The Sponsor submitted an interim REMS to address the risks of abuse, misuse, overdose, and addiction on March 24, 2010. The REMS includes a Medication Guide, Element to Assure Safe Use, specifically a plan to ensure Healthcare providers who prescribe OxyContin[®] will receive training under 505-1(f)(3)(A), and a timetable for submission of assessment of the REMS. We find the proposed REMS submitted on March 24, 2010, to be acceptable.

Once the elements of the class-wide opioid REMS are determined, the Sponsor will be notified to resubmit a REMS incorporating these elements, as was conveyed to the Sponsor in the June 17, 2009 Information Request letter.

1 BACKGROUND

1.1 INTRODUCTION

The proposed indication for OxyContin[®] is for the management of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. OxyContin[®] tablets are manufactured in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg dosage strengths. A single dose of OxyContin[®] greater than 40 mg, or a total daily dose greater than 80 mg are only for use in opioid-tolerant patients to avoid fatal respiratory depression. OxyContin[®] must not be cut, broken, chewed, crushed, or dissolved. Doing so can lead to rapid release and absorption of a potentially fatal dose of oxycodone. The clinical review of the clinical trials did not identify any unexpected adverse events, but did find the typical opioid-related adverse events.

A joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory committee was held on September 24, 2009. The joint committee was asked to discuss a) whether the studies performed by the sponsor adequately characterize the physical attributes of the reformulated OxyContin[®] product, b) whether the change in formulation affects the overall safety profile of

OxyContin[®] and c) whether this application for a reformulated OxyContin[®] should be approved.

The advisory panel consensus was that studies performed by the sponsor did adequately characterize the physical attributes of the reformulated OxyContin[®] product; however, many members expressed major concern with the lack of detail in the data presented by the sponsor. After discussing the effects of the change in formulation on overall safety, fourteen members voted to approve, four members voted not to approve, and one member abstained.

1.2 REGULATORY HISTORY

FDA approved OxyContin[®] Tablets (NDA 20-553), a controlled-release oral formulation of oxycodone hydrochloride on December 12, 1995. Due to the ongoing public health concerns indicating abuse and diversion of the current approved formulation of OxyContin[®], FDA and Purdue discussed the development of an abuse deterrent/abuse resistant formulation of OxyContin[®].

The sponsor submitted a RiskMAP on November 29, 2007 with the original NDA application for the reformulated OxyContin[®] product. A Complete Response (CR) letter was sent to the Sponsor on October 3, 2008 because the agency had determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary and in the CR letter a detailed description of the required elements of the proposed REMS were provided.

During the review of this NDA, the Agency was considering implementing a REMS across the class of modified-release opioids to address the risks of abuse and overdose and use in non-opioid tolerant individuals. Therefore, on December 4, 2008 the sponsor was sent a letter requesting that the sponsor not submit a Risk Evaluation and Mitigation Strategy (REMS) until the Agency notified the sponsor in writing about the elements necessary for a REMS across the class of modified-release opioids and that the Sponsor would be notified once that determination was made. .

On June 17, 2009, a General Correspondence Letter was sent to the Sponsor informing them that a class REMS for modified-released opioids would be implemented in the future. Until such a REMS was approved, Purdue Pharma was to submit a REMS that comprised of a Medication Guide, a Communication Plan, and a timetable for submission of assessments. The letter stated that once the elements of the class-wide REMS were determined, the sponsor would be required to submit a REMS incorporating these elements.

On July 23, 2009 (and amended on September 18, 2009 and November 13, 2009), Purdue submitted a proposed REMS in response to the general correspondence letter. After reviewing the proposed REMS and upon further consideration, the Agency determined that a Medication Guide and communication plan would not be adequate to ensure adequate training of healthcare providers to address the risks of abuse, misuse, and overdose. Therefore, on December 11, 2009, Purdue was notified that the REMS for OxyContin[®] (oxycodone hydrochloride controlled-release) must 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 controlled-release) outweigh

the risks. Subsequently, the Sponsor submitted proposed REMS amendments on December 21, 2009, February 4, 2010, and March 24, 2010.

2 MATERIAL REVIEWED

2.1 DATA AND INFORMATION SOURCES

1. General Correspondence Letter sent June 17, 2009
2. Proposed REMS submitted July 23, 2009
3. Proposed REMS amendment, submitted September 18, 2009
4. REMS notification letter sent December 11, 2009
5. Proposed REMS amendment (in response to REMS notification letter), submitted December 21, 2009.
6. Proposed REMS amendment, submitted February 4, 2010.
7. Proposed REMS amendment, with final REMS proposal submitted March 24, 2010.

2.2 ANALYSIS TECHNIQUES

The submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA) and the elements outlined in the REMS Notification Letter, as well as responsiveness to comments submitted to the Sponsor as part of the ongoing review.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

Safety concerns identified by the sponsor, DAAP and OSE are the potential for abuse, misuse, overdose, and addiction of OxyContin[®], as well as the risk of use of OxyContin[®] 60 mg and 80 mg tablets, or doses great than 40 mg, in non-opioid-tolerant individuals.

3.2 PROPOSED REMS

The March 24, 2010 final proposed REMS submission contains the following:

3.2.1 Goals:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin[®]
2. To inform patients and healthcare professionals about the safe use of OxyContin[®]

3.2.2 Medication Guide (MG)

In accordance with 21 CFR 208.24, a Medication Guide will be dispensed with each OxyContin[®] prescription. Purdue Pharma L.P. will ensure that the Medication Guide is available for distribution to patients receiving a prescription for OxyContin[®] by providing sufficient numbers to distributors and authorized dispensers.

1. One copy of Full Prescribing Information, which includes the Medication Guide, will be packaged with each bottle of OxyContin[®].
2. Two separate additional Medication Guides will also be packaged with each bottle of OxyContin[®].
3. Per 21CFR 208.24(d) the label of each container or package of OxyContin[®] will include a prominent and conspicuous statement:
 - a) instructing authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed (eg, “Attention Dispenser: Accompanying Medication Guide must be provided to each patient upon dispensing”), and
 - b) stating how the Medication Guide is provided.
4. Medication Guides will also be available via Purdue Pharma L.P. Field Sales representatives, through an Internet presence, and from Purdue’s Medical Services Department (1-888-726-7535).

3.2.3. Elements to Assure Safe Use

1. Healthcare providers who prescribe OxyContin[®] will receive training.
 - a. Purdue will ensure that training will be provided to healthcare providers who prescribe OxyContin[®]. To become trained, each prescriber will be provided with the OxyContin[®] Educational materials.

The Training includes the following:

- i) Proper patient selection;
- ii) Appropriate OxyContin[®] dosing and administration;
- iii) General principles of safe opioid use, including information about opioid abuse and how to identify patients who are at risk for addiction;
- iv) Potential abuse, misuse, overdose and addiction from exposure to opioids, including OxyContin[®];
- v) Risks of OxyContin[®], including:
 1. The risk of overdose caused by exposure to an essentially immediate-release form of oxycodone by consuming broken, chewed, crushed or dissolved OxyContin[®] tablets;
 2. The risk of addiction from exposure to OxyContin[®]; and

3. The risk of overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids from exposure to a single dose of OxyContin greater than 40 mg;
 - vi) Information to counsel patients and caregivers on the need to store opioid analgesics safely out of reach of children and household acquaintances and the need to properly dispose of unused drugs when no longer needed by the patient; and
 - vii) Importance of providing each patient a Medication Guide with each prescription and instructing the patient to read the Medication Guide.
- b. Purdue will ensure that at least 3 weeks prior to first availability of OxyContin[®] to healthcare professionals, a Dear Healthcare Professional letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose and addiction of OxyContin[®] as well as the need to complete the OxyContin[®] REMS Educational Program. This letter will be available on the Purdue website (www.OxyContinrems.com) for 1 year from the date of mailing.
- c. The mailings will include the following OxyContin[®] REMS Educational Program materials:
 - i) OxyContin[®] Medication Guide
 - ii) Prescribing OxyContin[®] Tablets CII: A Guide for Healthcare Providers
 - iii) OxyContin[®] Education Confirmation Form
- d. Additional printed educational material will be available through field-force distribution and by calling the toll-free number at Purdue (1-888-726-7535).
- e. The educational material will also be available for download at www.OxyContinrems.com.
- f. Purdue will maintain a list of all prescribers who have completed the OxyContin[®] REMS Educational Program.

Prescribers will be re-trained every two years or following substantial changes to the OxyContin[®] REMS. Substantial changes may include changes in the OxyContin[®]

Full Prescribing Information, OxyContin[®] Medication Guide, or OxyContin[®] REMS that require substantial modification of the educational materials.

The following materials are part of the REMS and are appended:

- Dear Healthcare Professional Letter
- Medication Guide
- The Healthcare Provider Guide, “Prescribing OxyContin[®] Tablets CII: A Training Guide for Healthcare Providers”
- OxyContin[®] Education Confirmation Form

Reviewer comment:

The Sponsor requested that the mailing date of the DHCP letter be closer to the date of first shipment [i.e., approximately three weeks prior to first shipment], rather than “within 60 days of approval” as was specified in the March 18, 2010 Discipline Review (DR) letter. DRISK consulted the Office of Compliance (OC) and they agreed to the alternate timeframe closer to launch but requested that the date of shipment of the DHCP letter/Educational materials and the number of mailings be included in the information needed for assessments.

3.2.4 Implementation System

Because OxyContin[®] can be approved without the Elements to Assure Safe Use described under FDCA 505-1(f)(3) (B), (C), and (D) of the Act, an implementation system is not required.

3.2.5. Timetable for Submission of Assessments

Purdue Pharma L.P. will submit REMS Assessments to FDA every 6 months for the first year from the date of approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Purdue L.P. will submit each assessment so that it will be received by the FDA on or before the due date.

The REMS Assessment Plan was summarized in the REMS Supporting Document and will be included in the approval letter. As part of the negotiations of the final OxyContin REMS, comments came from Office of Compliance regarding the information needed for Assessments and requested to include the date of the shipment of the DHCL letter and the number of mailings. The information needed for assessment will include at a minimum:

1. An evaluation of patients’ understanding of the serious risks of OxyContin[®].
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
4. A report on the status of the training program for healthcare providers including the number of Dear Healthcare Professional letters mailed to each specialty identified in the REMS, when the letters were mailed, and what information was included in the mailings.
5. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with OxyContin[®] (for example, through surveys of healthcare providers).
6. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
7. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.
8. A claims study to evaluate OxyContin[®] (oxycodone hydrochloride) utilization patterns including opioid-tolerant utilization patterns before and after implementation of the REMS.
9. 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.

Reviewer comments:

The Sponsor did not submit the survey instruments or methodologies. Without the survey instruments and methodologies there is insufficient information to complete a review of the patient and prescriber surveys. The Sponsor was informed on March 18, 2010 in a DR letter to submit for review the detailed plans that will be used to evaluate patients', prescribers', and pharmacists' understanding about the risks associated with and safe use of OxyContin[®] at least 90 days before the evaluation will be conducted. The submission should include all methodology and instruments that will be used to evaluate the knowledge about the risks associated with and safe use of OxyContin[®].

Upon further review it was determined that a pharmacist survey is not necessary as the target audience for the mailing and educational materials includes only prescribers. Please convey to the Sponsor that a pharmacist survey will not be necessary and refer them to the revised comments on the survey methodology (Appendix A).

4 DISCUSSION AND CONCLUSION

An interim REMS will be implemented by the Sponsor until a class-wide opioid REMS has been approved. The proposed REMS dated March 24, 2010 contains the required

REMS elements which includes a Medication Guide, element to assure safe use, and a timetable for submission of assessments.

The REMS Supporting Document outlines the information that the Sponsor will use to assess the effectiveness of the REMS in meeting the goals. The Sponsor did not submit the patient and prescriber survey instruments or methodologies; however, this information does not need to be submitted for FDA review prior to approval of the REMS. The DR letter of March 18, 2010 indicated that the Sponsor must submit for review the detailed plans that will be used to evaluate patients', prescribers', and pharmacists' understanding about the risks associated with and safe use of OxyContin[®] at least 90 days before the evaluation will be conducted. Please convey to the Sponsor that a pharmacist survey will not be necessary and to refer them to the revised comments on the surveys (Appendix 1). Please consult DRISK request once the survey instruments and methodologies have been submitted by the Sponsor.

Based on our current understanding of the risks of OxyContin[®], DRISK believes that a REMS comprised of these components is appropriate until a class-wide opioid REMS is established.

Appendix A: Revised Comments on Survey Methodology and Instruments

Submit for review the detailed plan that will be used to evaluate patients' and prescribers' understanding about the safe use of OxyContin[®]. The proposed plan **does not** need to be submitted for FDA review prior to approval of the REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodology and instruments that will be used to evaluate the knowledge about the risks associated with and safe use of OxyContin[®].

1. We encourage you to recruit respondents using a multi-modal approach. For example, respondents could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.

Explain how often non-respondent follow-up or reminders will be completed, and the planned frequency.

Explain how an incentive or honorarium will be offered, and the intended amount.

Explain how any recruitment sites will be selected.

Submit for review any recruitment advertisements.

2. Define the sample size and confidence associated with that sample size.
3. Define the expected number of people to be surveyed, and how the sample will be determined (selection criteria).
4. Explain the inclusion criteria for patients and prescribers; that is, who is an eligible respondent. For example, *patient* respondents might be:
 - Age 18 or older
 - Currently taking OxyContin[®] or have taken in past 3 months
 - Not currently participating in a clinical trial involving OxyContin[®]
 - Not a healthcare provider

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

5. Explain how often surveys will be administered, and the intended frequency.

Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, and in person.

Explain how surveyors will be trained.

6. Explain controls used to compensate for the limitations or bias associated with the methodology.
7. The sample should be demographically representative of the population who use the drug (patients), or prescribe the drug (doctors).

8. If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically.
9. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.

Potential respondents should be told that their answers will not affect their ability to receive or take (patients), prescribe (doctors); and that their answers and personal information will be kept confidential and anonymous.

10. Respondents should not be eligible for more than one wave of the survey.
11. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

Data may be stratified by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments that were utilized.

Regarding an assessment of patients' knowledge:

12. The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug; the assessment is not to evaluate consumer comprehension of the Medication Guide.

Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

13. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
14. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.

Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about OxyContin[®]?" section of the Medication Guide.

The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.

The order of the multiple choice responses should be randomized on each survey.

15. The order of the patient questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide.

Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

16. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

17. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with OxyContin[®]. The Medication Guide is a paper handout that contains important information about the risks associated with use of OxyContin[®] and how to use OxyContin[®] safely. Medication Guides always include the title “Medication Guide”.

18. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for OxyContin[®]? (Select all that apply)
 - My doctor or someone in my doctor’s office
 - My pharmacist or someone at the pharmacy
 - Someone else - please explain: _____
 - I did not get a Medication Guide for OxyContin[®]
- Did you read the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
- Did you understand what you read in the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
- Did someone offer to explain to you the information in the Medication Guide?
 - Yes, my doctor or someone in my doctor’s office
 - Yes, my pharmacist or someone at the pharmacy
 - Yes, someone else – please explain:

 - No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
 - All,

- Most,
 - Some,
 - None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

Regarding an assessment of healthcare providers’ (prescribers) knowledge:

19. The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating healthcare providers’ knowledge of: the serious risks associated with use of OxyContin[®], how to properly prescribe OxyContin[®], and how to properly monitor for the serious risks associated with the use of OxyContin[®]; the assessment is not to evaluate healthcare providers’ comprehension of the educational materials.

Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) again prior to taking the survey.

20. Submit for review the survey instruments (questionnaires and/or moderator’s guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

21. The healthcare provider knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials.

Questions should be non-biased, non-leading, multiple choice questions with the instruction to “select all that apply.” Each question should have an “I don’t know” answer option.

The order of the multiple choice responses should be randomized on each survey.

22. The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

23. Use the following (or similar) questions to assess receipt and use of the educational materials.

- Prior to today, which of the following were you aware of or received with regard to OxyContin[®]? (Select all that apply)

Educational Material	Aware	Received
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Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
Medication Guide	<input type="checkbox"/>	<input type="checkbox"/>
Dear Healthcare Provider Letter	<input type="checkbox"/>	<input type="checkbox"/>
Healthcare Provider Training Guide: Prescribing OxyContin	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

- Did you read the Full Prescribing Information?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the OxyContin[®] Full Prescribing Information
- Did you read the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the OxyContin[®] Medication Guide
- Did you read the Dear Healthcare Provider Letter?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the OxyContin[®] Dear Healthcare Provider Letter
- Did you read the Healthcare Provider Training Guide: Prescribing OxyContin?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the Training Educational Brochure for OxyContin[®]

- Do you have any questions about any of the educational materials related to Oxycontin? Yes or No (If Yes, list your question(s) below)
Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

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

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/s/

JEANNE P PERLA
04/02/2010

CLAUDIA B KARWOSKI
04/02/2010
concur

REMS Interim Review Comments

Drug Name:	BLA/NDA:	Date: 3-17-10
OxyContin (oxycodone hydrochloride controlled-release)	#22-272	Comment Set #3
DRISK Scientific Lead:		Reviewers:
Jeanne Perla, Ph.D., Risk Management Analyst		DRISK Gita Toyserkani, Pharm.D. Acting Team Leader Marcia Britt, Ph.D., Health Education Reviewer Jodi Duckhorn, MA, Social Science Reviewer
RCM #: 2009-788		

Materials Reviewed:

1. The following appended proposed REMS materials submitted on February 4, 2010 were reviewed:
 - a. Proposed REMS Document
 - b. Proposed REMS Supporting Document
 - c. Healthcare Professional Guide, “Prescribing OxyContin: A Healthcare Professional Guide”
2. Dear Healthcare Professional Letter received December 22, 2009

Introduction:

On December 11, 2009 Purdue received a REMS notification letter stating that a Medication Guide and Communication Plan would not be adequate to ensure adequate training of healthcare providers to address the labeled risks and to prevent the occurrence of serious adverse events associated with those risks. Purdue was informed that the REMS for OxyContin must contain a Medication Guide, an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), and a timetable for the submission of assessments of the REMS, to ensure that the benefits of OxyContin outweigh the risks. Purdue submitted an amended proposed REMS December 22, 2009 and February 4, 2010.

Comments for the Sponsor:

Please see **Appendix A (Appendix B – clean version)** for our revisions to the proposed REMS which is consistent with current Agency standards. The REMS Supporting Document must reflect the below changes to be consistent with the REMS document. Please incorporate the necessary revisions and include all current versions of materials in appendices in the next submission.

A. Goals

The Goals have been reviewed and found to be acceptable. We have minor editorial revisions.

B. Medication Guide

The Medication Guide has been reviewed and found to be acceptable.

C. Communication Plan

A communication plan is not a requirement of this proposed REMS; therefore, the proposed communication plan has been removed from the REMS document and applicable sections have been moved to corresponding sections in the “Elements to Assure Safe Use” in the REMS.

D. Elements to Assure Safe Use

1. The Dear Healthcare Professional (DHCP) Letter, previously submitted under the communication plan, will be included in the REMS under elements to assure safe use to inform healthcare professionals of the OxyContin REMS and the need for Healthcare Provider training. The previously submitted DHCP letter with minor edits is attached as **Appendix C**.
2. The DHCP letter must be mailed within 60 days of the approval of OxyContin® to prescribers most experienced in treating chronic pain with opioid agonists, including, pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of OxyContin®. The mailings must also include the OxyContin® REMS Educational Program materials.

Additional printed educational material should be made available through field-force distribution, by calling the toll free number, and available for download at the OxyContin® website.

3. The Agency finds the submitted revisions to the Healthcare Professional Guide to be acceptable.
4. As part of the healthcare provider training, develop a form that healthcare providers will return to the sponsor confirming they have completed the educational training. This form may request the following Prescriber Information:
 - (1) Prescriber name and credentials
 - (2) DEA Registration Number
 - (3) Specialty
 - (4) Affiliation
 - (5) Address
 - (6) Office Phone
 - (7) Office Fax
 - (8) Email

(9) Date form completed

We recommend that you include questions that can verify prescriber's understanding of the risks associated with OxyContin ER, the indication for use proper dosing, safety information about proper administration and storage of OxyContin ER, and the need for patient counseling

This form should include the following statement: "***Completion of this form does not affect your ability to prescribe OxyContin.***" Additionally, we require that you maintain a list of all prescribers that have completed the OxyContin® REMS Educational Program training and provide a report on the status of the training program as part of your REMS assessment.

E. Timetable for Submission of Assessment

The proposed timetable for submission of assessment is acceptable.

F. REMS Supporting Document

1. All Changes in REMS Document should be reflected in the REMS Supporting Document.
2. The following information needs to be included in your REMS Supporting Document under "Information Needed for Assessment:"
 - (1) An evaluation of patients' understanding of the serious risks of OxyContin.
 - (2) A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
 - (3) A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
 - (4) A report on the status of the training program for healthcare providers.
 - (5) An evaluation of healthcare providers' awareness and understanding of the serious risks associated with OxyContin (for example, through surveys of healthcare providers).
 - (6) Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
 - (7) An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.

- (8) A claims study to evaluate OxyContin (oxycodone hydrochloride) utilization patterns including opioid-tolerant utilization patterns before and after implementation of the REMS.
- (9) 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.

3. Survey Methodology:

Submit for review the detailed plan that will be used to evaluate patients', prescribers' and pharmacists' understanding about the safe use of Oxycontin. The proposed plan **does not** need to be submitted for FDA review prior to approval of the REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodology and instruments that will be used to evaluate the knowledge about the risks associated with and safe use of Oxycontin.

- (1) We encourage you to recruit respondents using a multi-modal approach. For example, respondents could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
- (2) Explain how often non-respondent follow-up or reminders will be completed, and the planned frequency.
- (3) Explain how an incentive or honorarium will be offered, and the intended amount.
- (4) Explain how any recruitment sites will be selected.
- (5) Submit for review any recruitment advertisements.
- (6) Define the sample size and confidence associated with that sample size.
- (7) Define the expected number of people to be surveyed, and how the sample will be determined (selection criteria).
- (8) Explain the inclusion criteria for patients, prescribers, pharmacists; that is, who is an eligible respondent. For example, patient respondents might be:
 - Age 18 or older
 - Currently taking Oxycontin or have taken in past 3 months
 - Not currently participating in a clinical trial involving Oxycontin
 - Not a healthcare provider

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

- (9) Explain how often surveys will be administered, and the intended frequency.
- (10) Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, and in person.
- (11) Explain how surveyors will be trained.
- (12) Explain controls used to compensate for the limitations or bias associated with the methodology.
- (13) The sample should be demographically representative of the population who use the drug (patients), prescribe the drug (doctors), or dispense the drug (pharmacists).
- (14) If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically.
- (15) Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
- (16) Potential respondents should be told that their answers will not affect their ability to receive or take (patients), prescribe (doctors), or dispense (pharmacists) the drug, and that their answers and personal information will be kept confidential and anonymous.
- (17) Respondents should not be eligible for more than one wave of the survey.
- (18) Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
- (19) Data may be stratified by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments that were utilized.

Regarding an assessment of patients' knowledge:

- (20) The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated

with use of the drug; the assessment is not to evaluate consumer comprehension of the Medication Guide.

Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

- (21) Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
- (22) The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.
- (23) Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Oxycontin?" section of the Medication Guide.
- (24) The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
- (25) The order of the multiple choice responses should be randomized on each survey.
- (26) The order of the patient questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.
- (27) Respondents should not have the opportunity or ability to go back to previous questions in the survey.
- (28) Explain if and when any education will be offered for incorrect responses.
- (29) Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
- (30) Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with Oxycontin. The Medication Guide is

a paper handout that contains important information about the risks associated with use of Oxycontin and how to use Oxycontin safely. Medication Guides always include the title “Medication Guide.”

(31) Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for Oxycontin? (Select all that apply)
 - My doctor or someone in my doctor’s office
 - My pharmacist or someone at the pharmacy
 - Someone else - please explain: _____
 - I did not get a Medication Guide for Oxycontin

- Did you read the Medication Guide?
 - All,
 - Most,
 - Some,
 - None

- Did you understand what you read in the Medication Guide?
 - All,
 - Most,
 - Some,
 - None

- Did someone offer to explain to you the information in the Medication Guide?
 - Yes, my doctor or someone in my doctor’s office
 - Yes, my pharmacist or someone at the pharmacy
 - Yes, someone else – please explain: _____
 - No

- Did you accept the offer? Yes or No

- Did you understand the explanation that was given to you?
 - All,
 - Most,
 - Some,
 - None

- Did or do you have any questions about the Medication Guide?
 - Yes (If Yes, list your question(s) below)
 - No

Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA.

Regarding an assessment of healthcare providers' (prescribers and/or pharmacists) knowledge:

- (32) The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating healthcare providers' knowledge of: the serious risks associated with use of Oxycontin, how to properly prescribe or dispense Oxycontin, and how to properly monitor for the serious risks associated with the use of Oxycontin; the assessment is not to evaluate healthcare providers' comprehension of the educational materials.

Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) again prior to taking the survey.

- (33) Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

- (34) The healthcare provider knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials.

Questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.

The order of the multiple choice responses should be randomized on each survey.

- (35) The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

(36) Use the following (or similar) questions to assess receipt and use of the educational materials.

- Prior to today, which of the following were you aware of or received with regard to Oxycontin? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
Medication Guide	<input type="checkbox"/>	<input type="checkbox"/>
Dear Healthcare Provider Letter	<input type="checkbox"/>	<input type="checkbox"/>
Healthcare Provider Training Guide: Prescribing OxyContin	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>
None of the above	<input type="checkbox"/>	<input type="checkbox"/>

- Did you read the Full Prescribing Information?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the Oxycontin Full Prescribing Information

- Did you read the Medication Guide?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the Oxycontin Medication Guide

- Did you read the Dear Healthcare Provider Letter?
 - All,
 - Most,

- Some,
 - None
 - I did not receive the Oxycontin Dear Healthcare Provider Letter
-
- Did you read the Healthcare Provider Training Guide: Prescribing OxyContin?
 - All,
 - Most,
 - Some,
 - None
 - I did not receive the Training Educational Brochure for Oxycontin

 - Do you have any questions about any of the educational materials related to Oxycontin?
 - Yes(If Yes, list your question(s) below
 - No

Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA.

G. General Comments:

Resubmission Requirements: Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document.

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

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/s/

JEANNE P PERLA
03/17/2010

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REMS Interim Review Comments

Drug Name:	BLA/NDA:	Date: 1-22-10
OxyContin (oxycodone hydrochloride controlled-release)	#22-272	Comment Set #3
DRISK Scientific Lead:		Reviewers: DRISK Jeanne Perla Ph.D Risk Analyst Gita Toyserkani PharmD Acting Team Leader Mary Willy Ph.D. Deputy Director Marcia Britt Ph.D. Health Education Reviewer DDMAC Mathilda Fienkeng PharmD, Regulatory Review Officer DPV Afrouz Nayernama PharmD, Safety Evaluator Office of Compliance Division of Risk Management and Surveillance Agnes Plante BSN, RN Consumer Safety Officer Suzanne Barone Ph.D. Team Leader for Risk Management and Strategic Problem Solving
Jeanne Perla		
RCM #: 2009-788		

Materials Reviewed:

- 1) Healthcare Professional Guide, “Prescribing OxyContin: A Healthcare Professional Guide”, included in the proposed REMS, received September 18, 2009
- 2) Discipline Review Letter, November 6, 2009
- 3) REMS notification letter, December 11, 2009
- 4) The following proposed material received December 22, 2009
 - a. REMS
 - b. Healthcare Professional Guide, “Prescribing OxyContin: A Healthcare Professional Guide”

Introduction:

On December 11, 2009, DAARP sent a REMS notification letter to Purdue Pharma. The notification letter specified that a Medication Guide and Communication Plan would not be adequate to ensure adequate training of healthcare providers to address the labeled risks and to prevent the occurrence of serious adverse events associated with those risks.

Purdue was informed that the REMS for OxyContin should contain a Medication Guide, an element to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), and a timetable for the submission of assessments of the REMS to ensure that the benefits of OxyContin outweigh the risks.

Purdue submitted a revised proposed REMS on December 22, 2009. The following comments provide additional comments on the submitted materials.

Comments for the Sponsor

A. Goals

The goals are acceptable.

B. Medication Guide

The Medication Guide has been reviewed and found to be acceptable. No revisions are expected at this time.

C. Communication Plan:

In the REMS notification letter dated December 11, 2009 you were notified that a Medication Guide and Communication Plan would not be adequate to ensure adequate training of healthcare providers to address the labeled risks and to prevent the occurrence of serious adverse events associated with those risks. You were required to submit a Medication Guide, elements to assure safe use [specifically healthcare provider training under 505-1(f)(3)(A)], and a timetable for the submission of an assessment of the REMS to ensure that benefits of OxyContin outweigh the risks of abuse, misuse, overdose, and addiction. We are not requesting a communication plan; therefore we are requiring you to remove this section of your submitted REMS. Letters can be sent out to targeted prescribers but will not be part of the REMS.

D. Elements to Assure Safe Use

1. REMS Template

- a. Move the following statement to Section B1b:
Prescribers will be re-trained every two years

2. Healthcare Provider Training Guide

- a. The black box warning has been removed from the revised training guide yet similar information is provided in the Important Safety Information. Place the black box warning back into the guide with verbatim language from the label.
- b. We compared the table of contents in the September 18, 2009 submission and think that the order of content from the September version is better than was submitted December 21, 2009. Revise the current brochure to follow the September 18, 2009 OxyContin Healthcare Provider Training Guide sequence.

- c. Include a purpose statement for the guide. The current guide reflects the goals of the REMS but doesn't clearly state a purpose for the guide. Example: The purpose of the Healthcare Provider Training Guide is to inform prescribers about important safety information about OxyContin to enable them to appropriately prescribe, dispense and counsel patients about the potential risk of misuse, abuse and addiction of OxyContin.

E. REMS Support Document

- a. Changes in REMS should be reflected in the Supporting Document.
- b. Assessments need to be consistent with those requested in the December 11, 2009. Example: It is not clear how Purdue is going to conduct a claims study to evaluate OxyContin utilization patterns including opioid-tolerant utilization patterns before and after implementation of the REMS.

General Comments:

Resubmission Requirements: Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22272

ORIG-1

PURDUE PHARMA
INC

OXYCONTIN

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/s/

JEANNE P PERLA

03/02/2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22272

ORIG-1

PURDUE PHARMA
INC

OXYCONTIN

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JEANNE P PERLA

03/10/2010

REMS Interim Review Comments

Drug Name:	BLA/NDA:	Date: 10-26-09
OxyContin CR (oxycodone hydrochloride controlled-release)	#22-272	Comment Set # 2
DRISK Scientific Lead:		Reviewers: DRISK Jeanne Perla Ph.D Risk Analyst Gita Toyserkani PharmD Acting Team Leader Mary Willy Ph.D. Deputy Director Marcia Britt Ph.D. Regulatory Health Specialist DDMAC Mathilda Fienkeng PharmD, Regulatory Review Officer DPV Afrouz Nayernama PharmD, Safety Evaluator
Jeanne Perla		
RCM #: 2009-788		

Materials Reviewed:

- 1) Information Request Letter, September 11, 2009
- 2) OxyContin Proposed REMS submitted September 18, 2009
 - a. Healthcare Professional Information Letter
 - b. Healthcare Professional Guide, “Prescribing OxyContin: A Healthcare Professional Guide”
 - c. Pharmacist Information Letter
- 3) OxyContin Proposed REMS Supporting Document submitted September 18, 2009

The comments below are Office of Surveillance and Epidemiology’s (OSE) review of the proposed REMS for OxyContin CR (oxycodone hydrochloride controlled-release).

Attached to this review includes an edited (with track changes) Proposed REMS, Information Letters to the Healthcare Providers, Pharmacist and Professional Associations, and Guide for Healthcare Providers.

Note to DAARP

Although the goals had been negotiated with the sponsor, we believe that it may be prudent to keep the goals for the interim opioid REMS the same as Embeda’s.

Comments for the Sponsor (also see attached document with track changes):

A. Goals

Goals should be:

- 1) to inform patients and providers about the potential for abuse, misuse, overdose, and addiction of OxyContin
- 2) to inform patients and providers about the safe use of OxyContin

B. Medication Guide

The Medication Guide has been reviewed and found to be acceptable. No revisions are expected at this time.

C. Communication Plan:

C.1 Information Letters (Healthcare Providers, Pharmacist and Professional Associations)

The sequence of the risk information within the letters minimizes the risks associated with OxyContin. For example, the precaution related to the use of OxyContin in

(b) (4)
is presented before warnings related to respiratory depression and severe hypotension. See the attached revised letters

C.2 Guide for Healthcare Providers (HCP)

1. Present the purpose of the guide towards the front. The healthcare provider should be able to open the guide and see the sponsor's rationale for providing them with this particular resource.
2. Introduction section- explain that REMS was created to educate prescribers about the potential risks associated with OxyContin which are reflected in the goals of the REMS. Follow this sentence with the goals.
3. The words in all caps can minimize the risk of other information provided. Despite being shown in the professional labeling in all caps this is promotion. Remove all caps (e.g., NOT, CONTRAINDICATED).
4. The box warning presented on page one of the HCP Guide is inconsistent with the current PI for OxyContin and could minimize the risks associated with OxyContin. Revise this section to be consistent with the PI.
5. The sequence of the risk information within the HCP Guide minimizes the risks being communicated and is inconsistent with the PI for OxyContin. For example, serious and common adverse effects are presented on page two of the HCP Guide, while warnings and precautions are presented on page three. Revise the sequence of the risk information within the HCP Guide to be consistent with the PI.
6. The HCP Guide fails to include material information regarding the REMS risks associated with OxyContin. For example, the HCP Guide presents risk information

related to use, misuse, accidental overdose, and addiction but omits the following statement from the PI:

- With parenteral abuse, the tablet excipients can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.
- Revise the HCP Guide to present REMS specific risk and material information.

D. Patient and provider surveys

Please submit for review a detailed plan to evaluate patients' and healthcare providers' understanding about the risks associated with and safe use of OxyContin. This information does not need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded "REMS Correspondence." The submission should include all methodology and survey instruments that will be used to evaluate the patients' and healthcare providers' understanding about the risks associated with and safe use of OxyContin. This should include, but not be limited to:

- Sample size and confidence associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients/healthcare providers to be surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with the methodology
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and correlation to the messages in the Medication Guide.

General Comments:

Resubmission Requirements: Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document. If certain documents

such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

The proposed REMS materials present claims such as, [REDACTED] (b) (4)
[REDACTED], and “[REDACTED]” (b) (4)
[REDACTED]” The proposed claims minimize the risks associated with OxyContin therapy. FDA recommends eliminating the language.

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/s/

MARY J DEMPSEY
10/29/2009

MARY E WILLY
10/29/2009
I concur

REMS Interim Review Comments

Drug Name: OxyContin (oxycodone hydrochloride controlled-release)	BLA/NDA: #22-272	Date: 09/4/09
		Comment Set # 1
DRISK Scientific Lead: Jeanne Perla		Reviewers: DRISK Jeanne Perla Mary Willy Marcia Britt DDMAC Mathilda Fienkeng
RCM #: 2009-788		

Materials Reviewed:

- 1) Information Request Letter, June 17, 2009
- 2) OxyContin Proposed REMS submitted July 23 2009
 - a. Healthcare Professional Information Letter
 - b. Healthcare Professional Guide, “Prescribing OxyContin: A Healthcare Professional Guide”
 - c. Pharmacist Information Letter
- 3) OxyContin Proposed REMS Supporting Document submitted July 23, 2009

Comments to DAARP:

We recommend changing the following language in the box and if you agree, that will need to be reflected in the letters and brochure:

Current language: oxycontin (b) (4)

Recommended language: oxycontin TABLETS MUST BE SWALLOWED...

Comments for the Sponsor (also see attached document with track changes):

I. Goals

- Goals 2 - Insert the words “the patient with” to read
Provide the patient with information on the proper use, storage, and disposal of OxyContin
- Delete Goals 3 and restate as Inform patients and providers about the potential for nonmedical use (ie, misuse, abuse and addiction) of OxyContin

II. Medication Guide

See attached REMS document with track changes.

III. Communication Plan:

Revise the Communication Plan as follows:

Add: In accordance with the United States federal Food, Drug, and Cosmetic ACT (FDCA) 505-1(e)(3), Purdue Pharma L.P. will execute a communication plan to HCPs to support implementation of OxyContin REMS for the first year following approval of the NDA for OxyContin.

Healthcare Professional Information Letter

1. The letter is not written in such a manner that important safety information is readily available to the healthcare professionals.
 - a. Bring important safety information to the top of the letter.
 - b. The risks associated with the misuse or abuse the drug is not clearly identified in the proposed letter.
 - c. Follow the goals in organizing the information provided. Begin with prescribing and dispensing information. Go on to briefly outline how the product should be stored and disposed of. Then discuss how prescribing, dispensing, storage and proper disposal contribute to the reduction in potential medical errors and nonmedical use. Patient counseling information should be provided further into the letter.
2. The information provided in the letter should be consistent with the label.
 - a. The proposed letter boxed warning states that OxyContin 60 mg, 80 mg, and 160 mg Tablet, or a single dose greater than 40 mg, **ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY**. The proposed label states that ‘OxyContin 60 mg and 80 mg, or doses greater than 40 mg ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY’. Determine the correct doses available and place this correct information in both the labeling and REMS.
3. Remove promotional references from the letter:
 (b) (4)
4. Refer the prescriber to the full prescribing information for details about important safety information.
5. Page 8 & 9 of the REMS Supporting Document - the sponsor states that the Dear Prescriber and Pharmacy Letter will be updated annually and sent to prescribers, as described above. Submit the letter to FDA for review after any updates are made. Sponsor needs to submit a timeline describing the duration of the letter’s dissemination from the time of launch.
6. The totality of the presentation within the Prescriber and Pharmacist information letters minimizes the REMS risks associated with OxyContin. The letters present the goals of the REMS program but omit specific risks related to  (b) (4)

(b) (4) and material information from the prescribing information (PI) on appropriate prescribing, dispensing, use, storage, and disposal of OxyContin. For example, the REMS related risk omissions include but are not limited to omission of the following statement:

(b) (4)

7. DDMAC recommends revising the letters to present ALL the REMS specific risk information and material information related to those risks **within the running text of the letter**.
8. Page two of the letter presents the statement, (b) (4) under the header, “*Contraindications for OxyContin*”.
 - a. DDMAC is concerned that this claim minimizes the risk being communicated by failing to clearly state that it is “contraindicated.” We note that the phrase (b) (4) . . .” is used only within the INDICATIONS AND USAGE section of the PI to describe types of pain for which the drug is not indicated.
9. The box should be removed and the information should be kept in the bullet format.
10. Provide the definition of opioid-tolerant patient not just tolerant to respiratory depressant effects of opioids.

Prescribing OxyContin: A Healthcare Professional Guide

1. The healthcare professional guide describes information already found in the full Prescribing Information. The new guide will need to be reduced in size. There are too many pages. The information is displayed as if it were the PI.
2. The sponsor states that there will not be an Element to Assure Safe Use; therefore, a REMS based-program name is not necessary. Delete all references to a program name.
3. The following recommendations are for the sponsor
 - a. Page two of the proposed guide includes the following claim, (b) (4)” (emphasis added)
 - DDMAC is concerned that this is an inadequate presentation of the indication for the drug. Specifically, the PI states, “*OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.*”
 - b. Page two of the proposed guide includes the following claim, (b) (4) (emphasis added)
 - DDMAC is concerned that the claim, “. . . , (b) (4) ” is promotional in tone and suggest that the REMS program is a benefit of the drug, and a voluntary action by Purdue.

Pharmacy Information Letter

1. Remove promotional references from the letter.
 - a. [REDACTED] (b) (4)
2. The totality of the presentation within the Prescriber and Pharmacist information letters minimizes the REMS risks associated with OxyContin. The letters present the goals of the REMS program but omit specific risks related to [REDACTED] (b) (4) and material information from the prescribing information (PI) on appropriate prescribing, dispensing, use, storage, and disposal of OxyContin. For example, the REMS related risk omissions include but are not limited to omission of the following statement,
[REDACTED] (b) (4)
4. DDMAC recommends revising the letters to present ALL the REMS specific risk information and material information related to those risks **within the running text of the letter.**
5. The proposed letter boxed warning states that [REDACTED] (b) (4)
[REDACTED] (b) (4)
The proposed label states that [REDACTED] (b) (4)
6. The contraindications provided in the proposed letter are not complete. Refer to the label.
 - a. Page two of each letter presents the statement, [REDACTED] (b) (4) . . .” under the header, “*Contraindications for OxyContin*”.
 - b. DDMAC is concerned that this claim minimizes the risk being communicated by failing to clearly state that it is “contraindicated.” We note that the phrase [REDACTED] (b) (4) . . .” is used only within the INDICATIONS AND USAGE section of the PI to describe types of pain for which the drug is not indicated.
7. The box should be removed and the information should be kept in the bullet format.
8. Provide the definition of opioid-tolerant patient not just tolerant to respiratory depressant effects of opioids

3. Timetable for Submission of Assessment

- Purdue Pharma L.P. will submit REMS Assessments to FDA every 6 months from the date of the approval of the REMS for the first year and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Purdue Pharma L.P. will submit each assessment so that it will be received by the FDA on or before the due date.

4. Supporting Document

Details of the surveys, including methodology and sampling were not provided and must be provided to FDA prior to implementation

General Comments:

- REMS do not address diversion. Remove the word (b) (4) “misuse” can be used
- Delete all reference to a REMS *program*
- Insert all references
- Submit letter to be sent to Physician and Other Healthcare Professional Associations.
- The proposed REMS materials present claims such as, “ (b) (4) and (b) (4) The proposed claims minimize the risks associated with OxyContin therapy. DDMAC recommends eliminating the language.
- DDMAC cannot comment on place holders such as, www.xxx.com

3 pp withheld in full immed. after this page as (b)(4) Draft Labeling.

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/s/

MARY J DEMPSEY
09/04/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH

DATE: April 3, 2008

FROM: Mary Willy, PhD
Division of Risk Management
Office of Surveillance and Epidemiology

THROUGH: Gerald Dal Pan, M.D., MHS, Director
Office of Surveillance and Epidemiology

TO: Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and
Risk Management Advisory Committee

SUBJECT: Risk Management of Opioid Drug Products and the New Formulation of
OxyContin

DRUG: OxyContin (oxycodone HCL controlled release) (NDA 22-272)

Overview of Risk Minimization Action Plans (RiskMAPs): RiskMAPs are strategies that try to balance benefit and risk of drugs and biologics by developing and implementing tools to minimize their risks while preserving their benefits. They include an ongoing evaluative process. RiskMAPs have been developed for certain opioids starting in the 1990s. Actiq was the first opioid drug product to be approved with a RiskMAP; it was approved in 1998 with a RiskMAP to ensure safe use of the product. A risk management plan was developed for Oxycontin about six years after its 1995 approval following reports that OxyContin was being abused for non-therapeutic purposes or for purposes other than those for which it was prescribed. In 2005, a guidance for industry on risk management recommended that sponsors of drug products under Schedule II of the Controlled Substances Act, including Schedule II extended release or high concentration opioid drug products, consider developing RiskMAPs.¹ On September 27, 2007 the Food and Drug Administration Amendments Act (FDAAA) was signed into law giving the FDA authority to require Sponsors to submit and implement a REMS if necessary to ensure that the benefits of a drug outweigh the risk of the drug.

Risk management of opioid drug products generally focuses primarily on three safety issues: 1) unintentional drug overdose, 2) accidental exposure, and 3) drug abuse, misuse, and diversion. More recently, efforts have begun to focus on minimizing improper patient selection. Unintentional drug overdose and improper patient selection are of concern with the high concentration opioid drug products that are supposed to be used in

¹ Guidance for Industry: Development and Use of Risk Minimization Action Plans.
<http://www.fda.gov/cder/guidance/6358fnl.htm>

opioid-tolerant patients. Accidental exposure is mostly related to inadvertent pediatric exposure, for example with Actiq. Drug abuse, misuse and diversion relate to all of the opioid drug products and are the most challenging risks to try to manage because these risks extend beyond the population the product is intended to treat.

All opioid risk management plans include educational efforts that are targeted to frequent prescribers of opioid drug products (information about the treatment of pain and identifying patients at risk for abuse), pharmacies (how to work with providers to detect abuse and diversion), and patients (information about addiction). Some Sponsors provide tamper-resistant prescription pads to help thwart fraud. Some RiskMAPs include monitoring for off-label use or use in inappropriate patients. Surveys of a sample of providers and/or patients about the drug's risks and key safety messages are being conducted by some Sponsors. All plans include some type of distribution chain security consistent with those required under the Controlled Substances Act.

Opioid risk management plans also include a surveillance component that is used to monitor for signals of abuse, misuse, and diversion. The databases used for monitoring include national databases such as SAMHSA's Drug Abuse Warning Network (DAWN Live!) and the Poison Control Database (also known as TESS). Many Sponsors also subscribe to RADARS (Researched Abuse, Diversion, and Addiction-Related Surveillance). RADARS collects data from four systems (Poison Control, Opioid Treatment, Key Informant and Drug Diversion).

Risk mitigation strategies that have been implemented for other non-opioid drugs include other elements to assure safe use such as limitations on the prescribing, dispensing and use of products to certain patients. These types of strategies are often developed for drugs when the products have established benefits, but also important risks. Currently there are no opioids that have limitations in the prescribing, dispensing or use beyond those restrictions established by controlled substance scheduling.

OxyContin Risk Management: Similar to other opioids, risk management for OxyContin includes educational and surveillance efforts. In past risk management reports the sponsor has provided summaries of their efforts, which have included the summary of some of their interventions when signals of abuse or diversion are identified. The recent submission for the new OxyContin formulation identifies the new formulation, which the sponsor claims is resistant to physical and chemical alterations, as a RiskMAP "tool" to reduce the abuse of OxyContin. The current NDA addresses only the 10, 15, 20, 30, and 40 mg tablets, but not the 60 or 80 mg formulations. The higher dosage strengths will be submitted following approval of the lower strengths. The sponsor proposes the following surveillance plan to monitor the effectiveness of this tool:

- 1) A secondary data analysis of RADARS Opioid Treatment Program Study using self-reported data on OxyContin abuse history from drug-addicted adults being treated in methadone treatment facilities. Investigators will compare four calendar quarters prior to the approval of the new formulation to four calendar quarters following approval of the new formulation to determine how many patients report past-month abuse of OxyContin.

Comments: Risk management of opioids is very challenging, particularly since one of the goals – to minimize abuse, misuse and diversion–involves individuals who may or may not have been prescribed the medication for a legitimate medical purpose. The development of a new formulation of OxyContin that is resistant to physical and chemical alterations might, in theory, be considered a new tool to manage these risks. The Office of Surveillance and Epidemiology has a number of concerns that relate to the management of the risk of abuse, misuse and diversion related to the new OxyContin formulation:

- Even if the new formulation is determined to be effective in minimizing abuse and misuse, the higher doses of OxyContin will not be re-formulated for some time and thus, remain a source for drug abusers to obtain high concentrations of OxyContin for abuse
- Although the new formulation OxyContin may discourage some people from abusing the drug by altering the formulation, the drug can still be abused in its unaltered state by taking large doses
- Prescribers may perceive the new formulation of OxyContin as *unabuseable* and preferentially prescribe the drug.

In addition to our concerns related to managing the risk of drug abuse with this newly formulated OxyContin, we also worry about certain unintended consequences of having different OxyContin products available. During the time that the lower strengths are on the market and the higher strengths are under review, we think there will be confusion among prescribers and pharmacists as to how to prescribe and dispense the drug when not all the oxycodone extended-release products will be re-formulated and we think that some prescribers may not know that the higher dosage forms of OxyContin are not re-formulated. Additionally there will be generic versions of the ‘old’ formulations still available. Lastly, as with all risk management strategies, it will be important to

measure the effectiveness of the new-formulation at reducing abuse, misuse and diversion. We recognize there are many challenges to monitoring abuse, particularly when there are multiple versions (generic, old formulation brand and now new formulation brand) and expect the evaluation of the introduction of a newly formulated OxyContin will require creative efforts. The proposed metrics include new evaluation strategies that have not been validated and, in our opinion, are not likely to provide clear evidence of effectiveness of the proposed risk management strategy.

Conclusion: Consideration of the new formulation of OxyContin will need to include a discussion of the extent that the re-formulation will effectively decrease abuse, misuse and diversion, the un-intended consequences that may result from the marketing of the new formulation, and the options for measuring the effectiveness of the new product's risk management program.

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/s/

Mary Dempsey
4/8/2008 12:03:28 PM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
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MEDICAL OFFICER