CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

POST-MARKETING OBSERVATIONAL STUDIES

NDA #:	22-272
Drug Name:	OxyContin (oxycodone hydrochloride)
Indication(s):	Management of moderate to severe pain
Applicant:	Purdue Pharma L.P.
Review Date(s):	October 5, 2012
Review Priority:	Standard
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Keywords: Observational studies, Drug abuse rates, GEE**,** interrupted time series

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1 EXECUTIVE SUMMARY

OxyContin (OC) was first approved by the Agency on December 12, 1995. OxyContin is a schedule II controlled substance with label indication, "For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." Oxycodone products are common targets for both drug abusers and drug addicts. The Agency approved the new reformulated OxyContin (ORF) in April 5, 2010. The new formulation of OxyContin was designed to make breaking, dissolving, crushing or chewing the tablet more difficult. Purdue ceased shipping the original formulation of OxyContin on August 5, 2010 and began shipping only reformulated tablets from August 9, 2010. As of January 2011, more than (b) (4) of filled prescriptions for OxyContin were reformulated OxyContin. At the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 21 and 22, 2010, Purdue proposed multiple post-marketing studies to assess the effects of reformulated OxyContin in the setting that reflects the actual usage. Purdue submitted preliminary reports on the studies as May 2012 to the Agency on July 31, 2012.

The Division of Epidemiology II requested the Division of Biometrics VII to review the preliminary report submitted in July 2012. This review provides a statistical evaluation of the design, methods and proposed analyses for studies 1, 2 and 6. An assessment of the preliminary results is also provided. However, a thorough and complete evaluation of the study results should be conducted upon the completion of the studies. A separate biostatistical review by Dr. Zhang addresses studies 3, 4, 5, and 11.

Study 1 was designed to investigate the routes and rates of OxyContin abuse among patients in substance abuse treatment programs in the ASI-MV Connect NAVIPPRO System. Specifically, patterns of past 30-day abuse of reformulated OxyContin (ORF) are compared to those of the original formulation (OC) after the introduction of ORF. In addition, the study assessed abuse through routes of administration (ROA) that require tampering, particularly snorting, injecting, and smoking. These were compared to original OxyContin and comparator opioids. The report covers preliminary analyses of the data from June, 1, 2009 to March, 31, 2012.

Generalized linear mixed model was used to estimate pre-ORF and post-ORF period percentages and relative percent change from the pre to post ORF period. Specifically, quarterly prevalence of past 30-day abuse for OC and ORF were compared to changes in comparator opioid analgesics ER morphine and ER oxymorphone. Although the data presented for 6 quarters post ORF is consistent with the study hypotheses of lower rates of abuse ORF, its profile compared to OC beyond the second quarter is very similar. The preliminary results show a considerable drop in levels of abuse through both oral and non-oral (smoking , snorting and injecting) after the introduction of ORF; however, with limited data points, the results do not support any substantial long term pattern.

Study 2 investigated the changes in rates of opioid overdose and poisoning (OOP) among patients dispensed OxyContin or comparator opioids in the Kaiser Permanente Northwest and Northern California regional health care systems before and after the introduction of

reformulated OxyContin (ORF). The study used chart abstraction data from February 2003 to July 2010, and 15 months following the introduction of ORF. The rates of OOP event associated with OxyContin use were compared to three groups of comparator opioids: a) other extended release opioids, b) immediate release, single entity oxycodone, and c) all other prescription opioids.

The findings at the time of this report do not suggest any substantial changes in dispense patterns or abuse rates or both. Data were only available for one full six-month period following the transition from the OC to ORF at this point. Limited data in the post-ORF period precludes the adequate assessment of the study results.

Study 6 used data from the Ohio Prescription Monitoring Program (PMP) and IMS LRx prescription database. The PMP study examined the number of individuals who obtained prescriptions by multiple prescribers and filled at multiple pharmacies. In the IMS LRx analysis, the goal was to assess the potential changes in the proportion of opioid shopping behavior among OxyContin users after the introduction of ORF. Doctor shopping was defined as a patient that visits multiple prescribers and pharmacies to obtain and fill more than necessary opioid prescriptions, in order to abuse or sell the excess opioids.

The PMP analysis consisted of data from August 8, 2008 to June 11, 2011. The IMS LRx analysis consisted of 2 six-month pre-periods (July to December 2009 and January to June 2010) and 2 six-month post-periods (January to June 2011 and July to December 2011). The PMP analysis used data from the Ohio Automated Rx Reporting System (OARRS). The study estimated the counts and rates of individuals who filled OxyContin prescriptions from a combination of 1-5 or more prescribers and 1-5 or more pharmacies. In IMS LRx analysis, the study used a database that consisted of patient de-identified longitudinal prescription from a sample of IMS Health retail and mail order prescriptions universe. Relative change in proportions was used to assess the shopping behavior of OxyContin from pre-ORF to post-ORF.

There are a total of 5 data points in the PMP analysis and 4 in the IMS LRx analysis. With very few data points, the analysis does not provide sufficient information to identify or establish a trend.

The design aspects of post-marketing observational studies on abuse deterrence were discussed in the Joint Meeting of the Anesthetic and Life Support Advisory Committee and the Drug Safety and Risk Management Advisory Committee in October 2010. The trend approach and the requirement of a sufficient period of time to establish the pattern of abuse and to demonstrate sustainability were emphasized by the committee. In order to properly characterize the abuse pattern over time, we need to be confident that the trend is stable and well characterized, which may require longer observation periods and the ability to consider the autocorrelation structure and possibly periodicity or seasonal patterns in the data. The accuracy, in terms of bias and variability, of the outcome measure would also affect the necessary length of the observational period. The three studies covered in this review had approximately 1 to 1.5 years of data after ORF was introduced into the market, corresponding to 2 to 6 data points depending on the data source. The adequacy of data points/structure for these studies should be further evaluated upon

the completion of the study. Therefore, the results presented in this preliminary study report do not provide conclusive evidence for the evaluation of abuse deterrence.

2 INTRODUCTION

2.1 Background

OxyContin (OC) was first approved by the Agency on December 12, 1995. OxyContin is a schedule II controlled substance with label indication, "For the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." Oxycodone products are common targets for both drug abusers and drug addicts. The Agency approved the new reformulated OxyContin (ORF) in April 5, 2010. The new formulation of OxyContin was designed to make breaking, dissolving, crushing or chewing the tablet more difficult. Purdue ceased shipping the original formulation of OxyContin on August 5, 2010 and began shipping only reformulated tablets from August 9, 2010. As of January 2011, more than (b) (4) of filled prescriptions for OxyContin were reformulated OxyContin. At the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on October 21 and 22, 2010, Purdue proposed multiple post-marketing studies to assess the effects of reformulated OxyContin in the setting that reflects the actual usage. Purdue submitted preliminary reports on the studies as May 2012 to the Agency on July 31, 2012.

As part of the post marketing requirement, the sponsor has conducted six epidemiology studies to assess the effects of ORF on patterns of abuse and misuse, and their consequences of addiction, overdose, and death. Additionally, the sponsor has conducted five supplemental studies or analyses of surveillance systems that provide additional information on the effects of ORF. The epidemiology studies were designed to assess the effects of ORF on patterns of abuse and misuse, and their consequences of addiction, overdose and death. Purdue submitted reports on the studies as May 2012 to the Agency on July 31, 2012.

The Division of Epidemiology II requested the Division of Biometrics VII to review the preliminary report submitted in July 2012. The purpose of this statistical review is to provide comments on the statistical approaches and results for the three observational studies as below:

- Study 1: Routes and Rates of OxyContin Abuse Among Patients in Substance Abuse Treatment Programs in the ASI-MV Connect NAVIPPRO System
- Study 2: Changes in Rates of Opioid Overdose and Poisoning Events in the Kaiser Permanente Health System with the Introduction of Reformulated OxyContin
- Study 6: Doctor-shopping for OxyContin as Measured by Prescription Monitoring Programs

A separate biostatistical review by Dr. Zhang addresses studies 3, 4, 5, and 11.

2.2 Material reviewed

OxyContin (oxycodone hydrochloride controlled-release) Tablets - Report on the Findings as of May 2012: Post-marketing Epidemiology Study Program to Assess the Effects of Reformulated Oxycontin on Patterns of Abuse and Misuse and their Consequences (Addiction, Overdose and Death), Patient Adverse Events, and Unintentional Exposures, July 2012, submitted on July 31, 2012 for NDA #022272.

2.3 Study Overview

- **Study 1:**
  This study was designed to investigate the routes and rates of OxyContin abuse among patients in substance abuse treatment programs in the ASI-MV Connect NAVIPPRO System. Specifically, patterns of past 30-day abuse of reformulated OxyContin (ORF) are compared to those of the original formulation (OC) after the introduction of ORF. In addition, the frequency of use of ORF as measured by number of days per month used was compared to that observed for original OxyContin and comparator opioids. In addition, the study assessed abused through routes of administration (ROA) that require tampering, particularly snorting, injecting, and smoking. These were compared to original OxyContin and comparator opioids. The report covers a preliminary analysis of the data from June, 1, 2009 to March, 31, 2012.

- **Study 2:**
  The study investigated the changes in rates of opioid overdose and poisoning (OOP) in the Kaiser Permanente Health System before and after the introduction of reformulated OxyContin (ORF). The study used chart abstraction data from February 2003 to July 2010 and 15 months following the introduction of ORF. Overall there were (b) (4) events, (b) (4) Kaiser Permanente Northwest (KPNW) and (b) (4) from Kaiser Permanente Northern California (KPNC).

  The objective was to estimate and compare rates of opioid overdose and poisoning (OOP) events before and after the introduction of ORF among individuals dispensed OxyContin. The rates are compared to individuals dispensed to three groups of comparator opioids: a) other extended release opioids, b) Immediate release, single entity oxycodone, and c) all other prescription opioids.

- **Study 6:**
  This study used data from the Ohio Prescription Monitoring Program (PMP) and IMS LRx prescription database. The PMP study examined the number of individuals who obtained prescriptions by multiple prescribers and filled at multiple pharmacies. In the IMS LRx analysis, the study used a database that consisted of patient de-identified longitudinal prescription from a sample of IMS Health retail and mail order prescriptions universe. The goal was to assess the potential changes in the proportion of opioid shopping behavior among OxyContin users after the introduction of ORF. Doctor shopping was defined as a patient that visits multiple prescribers and pharmacies to

obtain and fill more than necessary opioid prescriptions, in order to abuse or sell the excess opioids.

The PMP analysis consisted of data from August 8, 2008 to June 11, 2011 (5 data points). The IMS LRx analysis consisted of 2 six-month data in the pre ORF period (July to December 2009 and January to June 2010) and 2 six-month data in the post-ORF period (January to June 2011 and July to December 2011).

3 STATISTICAL EVALUATION

3.1 Study 1 (NAVIPPRO STUDY)

3.1.1 Study Overview

This study was designed to investigate the routes and rates of OxyContin abuse among patients in substance abuse treatment programs in the ASI-MV Connect NAVIPPRO System. Specifically, patterns of past 30-day abuse of reformulated OxyContin (ORF) are compared to those of the original formulation (OC) after the introduction of ORF. In addition, the frequency of use of ORF as measured by number of days per month used was compared to that observed for original OxyContin and comparator opioids. In addition, the study assessed abused through routes of administration (ROA) that require tampering, particularly snorting, injecting, and smoking. These were compared to original OxyContin and comparator opioids. The report covers preliminary analyses of the data from June, 1, 2009 to March, 31, 2012.

3.1.2 Study Design and Outcome Measures

This was an observational study designed to compare the prevalence, prescription-adjusted prevalence rates and route of administration (ROA) patterns of past 30-day abuse of ORF to that of OC before and after the introduction of ORF. These estimates were compared to changes in comparator opioid analgesics ER morphine and ER oxymorphone in the same period. The study used a stratified two-stage cluster design to sample respondents. First, the number of sites was determined. Second, the number of patients within sites that are needed to ensure a representative sample was obtained. Each respondent reported the abused compound and the route(s) in which the compound was abused. Past prevalence of abuse and ROA of OC measured from June 1, 2009 through August 8, 2010, about 5 quarterly data points were compared with ORF experience from August 9, 2010 through March 31, 2012 (6 quarterly data points).

The study examined the ROA patterns and abuse rates of ORF by four outcome measures:

- prevalence of past 30-day abuse among all respondents evaluated or within the subset of individuals reporting past 30-day abuse of any prescription opioid
- prescription-adjusted prevalence rates of abuse
- prevalence of abuse via oral and non-oral ROA for ORF, OC and comparator opioids
- frequency of abuse

Abuse and ROA patterns were captured via self-report during the ASI-MV interview which contains product-specific questions about abuse, routes and sources.

Comments:
The study employed an observational design that gathered information on opioid abusers before and after the introduction of the reformulated OxyContin. The proposed design is appropriate if limitations such as misclassification of abused compound; and selection bias due to the sample of sites are minimal. Although, we can capture the information of specific products and routes by self-report, social desirability bias is a problem with self-report measures and can affect the validity of the study.

3.1.3 Statistical Methodologies

The study used generalized linear mixed (GLMM) models to estimate pre-ORF and post-ORF period percentages and relative percent change from the pre to post ORF period. Logistic regression models, using the GLIMMIX procedure, were used to evaluate the percentages and relative percent change from the pre to post ORF. Also, log-binomial regression model was used to estimate the mean number of days of abuse and relative percent change in the mean number of days of abuse for pre-ORF and post-ORF period. The independent variables for the regression models include the main effects, two and three way interactions terms of opioid/drug indicator, ROA indicator, and time (per quarter). Random effects were used to account for multiple observations per ASI-MV respondent and nesting of respondents within a zip code.

Comments:
1. *Since the study collected repeated observations on respondents over time and clustered observations within sites, the GLMMs are appropriate to estimate the population-averaged outcome. More specifically, the outcome was the average change in respondents' responses before and after the introduction of ORF.*

2. *The form of the dependency (within respondents) does not usually affect parameter estimates as long as the regression models are correctly specified, however, we still recommend the sponsor to conduct sensitivity analyses for different specifications of the intra-cluster correlation matrix to assess the robustness of the study outcomes.*

3. *The analyses of seasonal effects were neither discussed in the protocol nor the interim report. GLMM model can handle seasonal effect either through various covariance structures or using sine cosine pairs in the model. The sponsor should first clarify if seasonal or temporal pattern exists in the data, if it does exist, then the appropriately scaled harmonic functions should be considered.*

4. *The dependent variables include time (per quarter). There are no discussions on how the time variable enters the model. Sponsor should clarify this and should also consider the transformations of time variable to properly capture the trends using the GLIMMIX procedure.*

3.1.4 Results and Conclusions

As indicated in the study report, the trend of OxyContin abuse (OC and ORF) via any ROA over the study period declined in the quarterly prevalence of past 30-day abuse following the introduction of ORF as a proportion of all assessments (Figure 9, page 34) and among prescription opioid abusers (Figure 10, page 35). With respect to ROA, the analysis yielded similar findings (Table 9, page 35; and Figures 11, 12, and 13, pages 39-41).

Comments:
We should interpret sponsor's results with caution for reasons stated below:

1. *Although, the levels of abuse declined in the first three quarters of post-ORF period, the levels of OC and ORF thereafter remains almost the same and showed consistent patterns for both OC and ORF. The abuse rate of OC in the post-ORF period is expected to drop gradually over time because of the limited supply. As stated in the report, prescriptions filled at pharmacies for original OxyContin constituted* (b) (4) *of total OxyContin prescriptions in January 2011, June 2011 and December 2011, respectively. The limited supply of original OxyContin from prescriptions filled at pharmacies is unlikely to account for the continued levels of abuse of OC. Some degree of misclassification between OC and ORF exists; therefore, the study results are subject to misclassification bias.*

2. *The study results are based on an interim analysis and should be interpreted within the time frame and limited data provided. An explicit explanation on how the sponsor intends to further investigate this issue is encouraged. As noted in the study report, the results are preliminary and abuse patterns may change over time. Therefore, a complete assessment of pre and post ORF may require a longer period.*

3.1.5 SUMMARY AND CONCLUSIONS

Self-report captures specific products and routes but social desirability bias is a problem with self-report measures and can affect the validity of the study. Although the use of ASI-MV sentinel surveillance sample provides a sensitive population with a high potential of drug abuse, it is not a random sample. Therefore, the preliminary results and results upon the completion of the study may not be generalized to broader population.

Although the data presented for 20 months post ORF is consistent with the study hypotheses of lower rates of abuse ORF, its profile compared to OC beyond the second quarter is very similar. The preliminary results shows a considerable drop in the level of ROA after the introduction of ORF, however the results do not support any substantial long term pattern. Because the observation period is short, long term patterns can not be assessed with the preliminary data.

The statistical analysis employed in the study appears appropriate for the study design. However, it is not clear how the time variable is used to capture trends in the data. Also, the analyses on seasonal effects with respect to the GLMM model are not discussed. Since data were collected from (b) (4) centers with multiple reports of routes of administration from respondents, sensitivity analysis of different specifications of the intra-cluster correlation matrix are recommended.

In addition to the results presented in the Table 10, it is recommended that the investigators include the number of unique respondents by quarter. Also, investigators may add summaries of unique respondents that contributed to multiple ROA.

3.2 Study 2 (KAISER STUDY)

3.2.1 Study Overview

The study investigated the changes in rates of opioid overdose and poisoning (OOP) in the Kaiser Permanente Health System before and after the introduction of reformulated OxyContin (ORF). The study used chart abstraction data from February 2003 to July 2010 and 15 months following the introduction of ORF. Overall there were (b) (4) events, (b) (4) Kaiser Permanente Northwest (KPNW) and (b) (4) from Kaiser Permanente Northern California (KPNC).

The objective was to estimate and compare rates of opioid overdose and poisoning (OOP) events before and after the introduction of ORF among individuals dispensed OxyContin. The rates for individuals dispensed to OC/ORF are compared to those for individuals dispensed to three groups of comparator opioids: a) other extended release opioids, b) Immediate release, single entity oxycodone, and c) all other prescription opioids.

3.2.2 Study Design and Outcome Measures

An interrupted time series design was used to longitudinally compare rates of OOP events associated with OxyContin to rates of OOP events associated with other oxycodone and opioid formulations over a 10-year period. Specifically, an interrupted time series approach and a ratio of risk ratios approach is used to compare trends in rates of OOP events before and after the introduction of ORF. For the proposed ITS analysis, abuse rates of OxyContin in six-month interval would be compared to immediate-release single ingredient oxycodone, other long-acting opioids, and other Schedule II opioids. The computed rates cover a period of seven years before ORF and 2.5 years post-ORF.

The poisonings and overdoses rates associated with OxyContin were computed as follows:

- Number of poisonings/overdoses for people with a dispense of OxyContin/oxycodone ER divided by the number of people with a dispensing of OxyContin/oxycodone ER and
- Number of poisonings/overdoses for people with a dispense of OxyContin/oxycodone ER divided by Morphine equivalent milligrams of all dispenses of OxyContin/oxycodone ER

A proposed analysis to examine the rate of OOP events per person time exposed to OxyContin is defined as

- The ratio of the number of poisonings/overdoses for people with a dispensing of OxyContin and person time on OxyContin

Person time on OxyContin is defined as the number of days on OxyContin for people dispensed OxyContin in a given six-month period. Similar rates were computed for immediate release single ingredient oxycodone, other class REMS opioids, and other Schedule II opioids for each

six-month period. The three specified rates will be used to determine the changes in trends of the rate of OOP events after the new formulation.

Comments:

1. *The proposed study design compares the rates of OOP events in OxyContin to that of other opioids after the introduction of ORF. The comparable opioids were neither reformulated before or after the introduction of ORF. Therefore, the design appropriately separates the effects due to the introduction of ORF from the effects that may have occurred at that time.*

2. An important measure of the interrupted time series analysis is the difference between the predicted behavior in post- ORF phase (using pre-ORF series) and the actual (observed) behavior of the series in the post- ORF phase. Therefore, we recommend that the sponsor present the results (predicted estimates) of post-ORF using pre-ORF data and summaries of the actual post-ORF data.

3.2.3 Statistical Methodologies

The study proposes to use an interrupted time series (ITS) approach and a ratio of risk ratios approach (RR). The ITS approach models the rate of OOP from February, 2003 to July, 2010 as phase 1 and compares its estimates to that of phase 2 from August, 2010 to December, 2012.

Comments:

In the proposed ITS approach, rates are calculated in six-month intervals for a period of 10 years. Seven years of data prior to ORF introduction are compared to 2.5 years after ORF, i.e., 14 data points in pre-ORF vs. 5 data points in post-ORF. In order to properly characterize the abuse pattern over time, sufficient number of data point is required to account sufficiently characterized the trend and serial dependency (autocorrelation), and also possibly the seasonal or temporal pattern in the data. The accuracy, in terms of bias and variability, of the outcome measure would also affect the observational period. Simulation studies (Crosbie, 1993) indicates that the estimate of autocorrelation is unreliable with fewer data points, leading to an inflated type II error, i.e., insufficient power. The adequacy of data points/structure for this study will be further evaluated upon the completion of the study.

3.2.4 Results and Conclusions

According to the study report, " At the time of this report, data were only available for only one full six- month period following the transition from the original to the new formulation of OxyContin." Prior to the transition period, the dispense patterns of OxyContin showed an upward trend from 2003 to 2008. However, the pattern declined rapidly through the transition period and thereafter (Figures 14 and 18, pages 64 and 69 respectively). Therefore, the only data point post-ORF may not be exclusive.

Also, the results presented in Tables 25 and 26 do not indicate any considerable difference in OOP event rates. The findings at the time of this report do not suggest any substantial changes in dispense patterns or abuse rates or both.

Comment:

Data were only available for one full six-month period following the transition from the OC to ORF at this point. Therefore, limited information precludes the adequate assessment of the study results. We will not comment further on the study results of the preliminary report.

3.2.4 SUMMARY AND CONCLUSIONS

The proposed analyses cover a period of six-month intervals for 10 years. Seven years prior to the new OxyContin formulation are compared to 2.5 years after the new formulation. The chosen intervals result in 14 data points in pre-ORF and 5 data points in post- ORF. With fewer data points, the estimates of variability, serial dependency and visual inference are not reliable. Therefore, no meaningful conclusions can be drawn from such analyses.

The proposed design appropriately separates the effects due to the introduction of ORF from the effects that may have occurred at that time. With only one six-month data in the post-ORF period, there is not enough information to adequately assess the results of the study. The findings at the time of this report do not suggest any substantial changes in dispense patterns or abuse rates or both. Therefore, no conclusions can be drawn from this preliminary study report.

In addition to the results presented in Tables 25 and 26, it is recommended that the following are included: the number of OOP events, unique persons that contributed the person time analysis.

3.3 Study 6 (PMPs STUDY)

3.3.1 Study Overview

This study used data from the Ohio Prescription Monitoring Program (PMP) and IMS LRx prescription database. The PMP study examined the number of individuals who obtained prescriptions by multiple prescribers and filled at multiple pharmacies. In the IMS LRx analysis, the study used a database that consisted of patient de-identified longitudinal prescription from a sample of IMS Health retail and mail order prescriptions universe. The goal was to assess the potential changes in the proportion of opioid shopping behavior among OxyContin users after the introduction of ORF. Doctor shopping was defined as a patient that visits multiple prescribers and pharmacies to obtain and fill more than necessary opioid prescriptions, in order to abuse or sell the excess opioids.

3.3.2 Study Design and Outcome Measures

The study utilizes an open cohort design that compares changes in doctor-shopping for OxyContin and comparator opioids over time. The study population consisted of residents of the

states whose prescriptions are reported into the PMPs that participated in the study. The participated states considered in the study are Connecticut, Ohio and Massachusetts. The interim report discussed the results based on the Ohio PMP and a sample from national database referred to as IMS LRx prescription database. The IMS LRx prescription database consisted of patients de-identified longitudinal prescriptions from a sample of IMS Health retail and mail order prescriptions universe.

The PMP analysis estimated counts of individuals who obtained OxyContin from a combination of 1-5 or more unique pharmacies and 1-5 or more unique prescribers. In the IMS LRx analysis, changes in shopping proportions from pre-ORF to post-ORF, expressed as relative change in proportions, were calculated as:

> [(Proportion of Patients with Overlap Events in Jul-Dec 2011) – (Proportion of Patients with Overlap Events in Jan-Jun 2010)] ÷ (Proportion of Patients with Overlap Events in Jan-Jun 2010).

Comments:

The study used an open cohort design that compared doctor shopping behavior among OxyContin patients before and after the introduction of ORF. This design seems appropriate since the individual "shoppers" define the date of entry and exit within the 6-month periods. Also the size of the study population is not constant. Therefore, the use of counts and proportions as the outcome measure for OxyContin shopping may be reasonable. However, the limited number of data points does not allow for trend analysis.

3.3.3 Statistical Methodologies

In the PMP analysis, the study estimated the counts and rates of individuals who filled OxyContin prescriptions from a combination of 1-5 or more prescribers and 1-5 or more pharmacies. In IMS LRx analysis, the study used relative change in proportions to assess the shopping behavior of OxyContin from pre-ORF to post-ORF. To test for significant change in shopping proportions, a relative risk and a 95% confidence limit were estimated.

Comments:
The use of rates, and relative risk with 95% confidence limits is reasonable for the proposed study. However, the method to compute 95% CI was not specified in the report. The sponsor should clarify which method is used to compute the 95% CI, especially the low event rate is observed in certain groups.

3.3.4 Results and Conclusions

The results of the PMP analysis indicate that there is no difference in counts and rates of doctor shopping before and after the introduction of ORF.

Comments*:*

Although, findings from the IMS LRx analysis show a reduction in doctor shopping for OxyContin, the evidence is misleading. First, the results solely depends on the cut-offs used in combining the numbers of prescribers and pharmacies. These cut-off criteria lack standard support. In addition, 5 six-month periods in the PMP analysis and 4 six-month periods in the IMS LRx analysis are not enough to assess the level and slope of doctor shopping behavior

3.3.5 SUMMARY AND CONCLUSIONS

There are a total of 5 data points in the PMP analysis and 4 data points in the IMS LRx analysis. Limited information precludes the adequate assessment of the study results. In addition, the results depend on the cut-off used in combining the numbers of prescribers and pharmacies. Sponsor should provide justification which cut-off criterion should be the primary measure(s). The results of outcome measures, i.e., rate, over time were not presented in the study report; therefore, the assessment of trend cannot be performed for this study.

Reference

Crosbie J., *Interrupted time-series analysis with brief single-subject data:* Journal of Consulting and Clinical Psychol. 1993 Dec;61(6):966-74

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Food and Drug Administration
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Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NDA/BLA Number:	NDA 22272
Drug Name:	OxyContin (oxycodone hydrochloride)
Indication(s):	Management of moderate to severe pain
Applicant:	Purdue Pharma, L.P.
Date(s):	November 1, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 7
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Keywords: Observational studies, drug abuse and diversion rates, negative binomial model, interrupted time series

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

OxyContin (oxycondone hydrochloride) is a schedule II, long-acting opioid agnoiste indicated for the management of moderate to severe pain. The product was first approved in 1995. Purdue Pharma L.P. (the sponsor) reformulated OxyContin in 2010 with the goal of making the product more difficult to abuse. As part of the post marketing requirement, the sponsor has conducted eleven observational studies to assess the effects of the reformulated OxyContin (ORF) on patterns of abuse and misuse, and their consequences of addiction, overdose, and death. The Division of Epidemiology II requested the Division of Biometrics VII to review the study report submitted by the sponsor in July 2012.

This statistical review focuses on four studies, i.e., Study 3 (RADARS Poison Centers), Study 4 (National Surveys), Study 5 (RADARS Drug Diversion Program), and Study 11 (National Poison Data System).

The basic design for these studies is to assess changes from before and after the introduction of ORF, and compare changes for OxyContin to changes for comparator opioids. Various outcomes on abuse and diversion from different data sources were reported for OxyContin and comparator opioids by quarters from 2008-Q4 to 2011-Q4 or 2012-Q1 depending on the data source. Negative binomial regression was used to evaluate the effect of ORF. However, details on the model specification and the corresponding hypothesis tests were not provided in the report. Therefore, without the explicit description for the statistical approach, the statistical reviewer cannot provide comments on the analysis results.

Several limitations were found in these studies. First, in all studies, the reported numbers of abuse and drug diversion for OxyContin during the post-ORF period include events for both original and reformulated OxyContin. Therefore, the actual effect of ORF was not properly estimated. Other limitations include the potential under-reporting and misclassification biases for the outcomes in the surveillance system and self-reported surveys.

Finally, in order to properly characterize the abuse pattern over time, we need ensure that the trend is stable and well characterized and to consider the autocorrelation structure and possible periodical or seasonal patterns in the data. The accuracy, in terms of bias and variability, of the outcome measure would also affect the length of necessary observational period. The four studies covered in this review had only 1 to 1.5 years of data after ORF was introduced into the market, which corresponds to 5-6 data points. The adequacy of data points and structure for these studies should be further evaluated upon the completion of the study. Therefore, the results presented in this preliminary study report do not provide conclusive evidence for the evaluation of abuse deterrence.

2. INTRODUCTION

2.1 Background

OxyContin (oxycondone hydrochloride) is a schedule II, long-acting opioid agnoiste indicated for the management of moderate to severe pain. The product was first approved in 1995. Problems with abuse and misuse were observed, and Purdue Pharma L.P. (the sponsor) reformulated OxyContin to have more tamper resistant properties compared to the original OxyContin. The reformulated OxyContin (ORF) was designed to be bioequivalent to the original formulation and to make the tablet more difficult to manipulate for the purpose of intentional misuse and abuse. FDA approved ORF in April 2010. The sponsor discontinued the original formulation and began shipping only ORF into the market in August 2010.

As part of the post marketing requirement, the sponsor has conducted six epidemiology studies to assess the effects of ORF on patterns of abuse and misuse, and their consequences of addiction, overdose, and death. Additionally, the sponsor has conducted five supplemental studies or analyses of surveillance systems that provide additional information on the effects of ORF. The sponsor submitted the protocols for its post-marketing epidemiology program in January 2011, an interim report on these studies in November 2011, and an update on these studies in July 2012. The Division of Epidemiology II requested the Division of Biometrics VII to review the updated report on seven studies (studies 1, 2, 3, 4, 5, 6, 11) submitted in July 2012. The purpose of this statistical review is to provide comments on the statistical approaches and results for the four observational studies as below:

- Study 3: Exposures Reported to Poison Centers in the RADARS System.
- Study 4: Using Surveys to Assess the Impact of Reformulated OxyContin.
- Study 5: Law Enforcement Events in the Drug Diversion Program of the RADARS System.
- Supplemental Study 11: Changes in Poison Center Exposure Rates for OxyContin, other SE oxycodone and heroin in the National Poison Data System.

A separate biostatistical review addresses studies 1, 2 and 6 to be performed by Dr. Frimpong independently.

2.2 Material reviewed

The following materials were reviewed:

- OxyContin (oxycodone hydrochloride controlled-release) Tablets - Report on the Findings as of May 2012: Post-marketing Epidemiology Study Program to Assess the Effects of Reformulated Oxycontin on Patterns of Abuse and Misuse and their Consequences (Addiction, Overdose and Death), Patient Adverse Events, and Unintentional Exposures, July 2012, submitted to DARRTS on July 31, 2012 for NDA #022272.
- The Appendices to the report of July 2012, submitted to DARRTS on July 31, 2012 for NDA #022272.

2.3 Overview of the Four Observational Studies

The four post-marketing observational studies were designed to assess the effect of reformulated OxyContin with different outcomes and data sources. The basic design for these studies is to assess changes in abuse-related outcomes from before to after ORF introduction, and to compare changes for OxyContin to changes for comparator opioids.

Study 3 and Study 11 assessed the intentional and unintentional exposure cases reported to Poison Centers covered in RADARS System and National Poison Data System respectively. Study 4 used three national surveys to estimate the non-medical use. Study 5 examined drug diversion cases reported to the RADARS System Drug Diversion Program. As most outcomes were summarized by quarters, there are 5 to 8 data points available in pre- or post-ORF up to the date of the report depending on different data sources. The limited numbers of data points preclude the statistical evaluation on the trend. In addition, results for some proposed primary outcomes were missing in the report. The following table provides a summary of the characteristics of the four studies.

Study 3 and Study 5 have many similarities. They used two programs from the same data source – the RADARS System, one for Poison Center Program and one for Drug Diversion Program. Although the outcomes of interest are different, the two studies used the same statistical method, negative binomial regression, to evaluate the outcomes. Therefore, we consider these two studies together in this statistical review.

Table 1: Summary of the Characteristics of the Four Observational Studies

	Study 3 (RADARS-Poison Centers)	Study 4 (National Surveys)	Study 5 (RADARS-Drug Diversion)	Study 11 (National Poison Data System)
Objectives[a]	• To estimate the change in the rate of intentional and unintentional exposure cases for OxyContin and comparator opioids before and after the introduction of ORF. • To assess changes in case fatality rates for OxyContin and comparator opioids before and after the introduction of ORF. • To compare the mortality rate for OxyContin for the period before and after the introduction of ORF to that for comparator opioids.	To estimate trends in the prevalence of abuse of OxyContin and other pharmaceutical opioids for the period before and after the introduction of ORF.	• To compare the rate of drug diversion cases for OxyContin and comparator opioids before and after the introduction of ORF. • To compare average street prices for OxyContin and comparator opioids before and after the introduction of ORF	To assess changes in Poison Center Exposure Rates for OxyContin, other SE Oxycodone and heroin with the introduction of ORF.
Data Source[b]	RADARS System Poison Center Program	1. National Survey on Drug Use and Health (NSDUH) 2. Monitoring the Future survey (MTF) 3. RADARS System College Survey (RADARS-CS)	RADARS System Drug Diversion Program	American Association of Poison Control Centers' National Poison Data System
Data Available	2008Q4 to 2012Q1	2009Q3 to 2011Q4	2008Q4 to 2012Q1	2009Q3 to 2011Q4
Data Points	8 points pre-ORF and 6 points post-ORF	5 points pre-ORF and 5 points post-ORF	8 points pre-ORF and 6 points post-ORF	5 points pre-ORF and 5 points post-ORF
Outcomes Proposed[c]	• Intentional exposures of OxyContin and comparator opioids • Fatalities with OxyContin and comparator opioids • Unintentional exposures of OxyContin and comparator	Past year non-medical use of OxyContin and other opioids, frequency of use, recent onset, persistence, DSM-IV dependence.	• Counts of drug diversion cases • Street prices	Exposures to OxyContin, heroin, and SE oxycodone (excluding OxyContin) based on calls to poison centers by individual callers or reported to poison centers by emergency departments. Intentional exposures

	opioids • Total exposures of OxyContin and other opioids			are defined as a purposeful action that results in an exposure. Unintentional exposures are defined as an exposure that results from an unforeseen or unplanned event.
Outcomes Reported	• Intentional abuse • Unintentional therapeutic errors • Intentional exposures • Unintentional general exposures of OxyContin, SE IR oxycodone, and other prescription opioids	Non-medical use of OxyContin, other IR oxycodone, and other prescription opioids	Drug diversion for OxyContin, other IR oxycodone, and other prescription opioids	• Intentional abuse • Unintentional therapeutic errors • Unintentional general exposures of OxyContin, SE ocycondone, and heroin. • Intentional exposure, unintentional exposure, adverse reactions, withdrawal, unknown, and total exposures of OxyContin (average exposures for pre- and post-ORF)
Denominators for Rates Reported	• Estimated US population covered in RADARS Poison Centers • Unique recipients of dispensed drug (purchased from IMS Health)	No rates were reported.	• Estimated US population covered in RADARS Drug Diversion Program	• Estimated US total population • Number of prescriptions (purchased from IMS Health)
Designs Proposed[d]	Observational Poisson interrupted time series	Repeated cross-sectional surveys	Observational Poisson interrupted time series	Longitudinal observational study
Analysis Method Used	Negative binomial regression	Negative binomial regression	Negative binomial regression	Descriptive statistics only

[a,b,c,d] The sponsor's statements in the study synopses (see Table 25, 29, 32, and 68 in the sponsor's report)

3. STATISTICAL EVALUATION

The design aspects of post-marketing observational studies on abuse deterrence were discussed in the FDA joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee in October 2010. The trend approach and the requirement of a sufficient period of time to establish the pattern of abuse and to demonstrate sustainability were emphasized by the committee. The committee's consensus was that a three year minimum observation period was necessary to demonstrate sustainability of the effects of an abuse-deterrent product[1].

In order to properly characterize the abuse pattern over time, we need ensure that the trend is stable and well characterized and to consider the autocorrelation structure and possible periodical or seasonal patterns in the data. The accuracy, in terms of bias and variability, of the outcome measure would also affect the length of the observational period. The four studies covered in this review had only 1 to 1.5 years of data after ORF was introduced into the market, i.e., 5-6 data points. The adequacy of data points/structure for these studies should be further evaluated upon the completion of the study. Therefore, the results presented in this preliminary study report do not provide conclusive evidence for the evaluation of abuse deterrence.

Several limitations were found in these studies. First, in all studies, the reported numbers of abuse and drug diversion for OxyContin during the post-ORF period include events for both original and reformulated OxyContin. Therefore, the actual effect of ORF was not properly estimated because the reported abuse and drug diversion rates after the introduction of ORF estimated the combined effects for original and reformulated OxyContin. Other limitations include the potential under-reporting and misclassification biases for the outcomes in the surveillance system and self-reported surveys.

3.1 Study 3 (RADARS - Poison Centers) and Study 5 (RADARS – Drug Diversion)

3.1.1 Outcomes

Study 3 focused on two outcomes: abuse and therapeutic errors. The numbers of abuse and therapeutic errors were obtained from the RADARS System Poison Centers Program for the following opioid products: OxyContin, other prescription opioids, and immediate release (IR) single entity (SE) oxycodone. These numbers were each divided by population or unique recipients of dispensed drug (URDD), yielding exposure rates per 1,000,000 population or per 10,000 URDD for OxyContin and comparator opioids. The population was the covered population by the RADARS Poison Center. The URDD was purchased from IMS Health.

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[1] Minutes for the October 12-22, 2010: Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting.
http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM236242.pdf

Study 5 focused on one outcome: drug diversion. The numbers of diversion were obtained from the RADARS System Drug Diversion Program for the following opioid products: OxyContin, other prescription opioids, and immediate release (IR) oxycodone.

Similar to Study 3, these numbers were each divided by population or unique recipients of dispensed drug (URDD), yielding exposure rates per 100,000 population or per 1,000 URDD for OxyContin and comparator opioids. The population was the covered population in the RADARS Drug Diversion Program.

Reviewer Comments:
The outcome measure reported in the study report were not consistent with those defined in the study protocol[2]*. In RADARS Poison Center Program, abuse is a subset of intentional exposures which consist of abuse, misuse, suspected suicide, and unknown; therapeutic error is a subset of unintentional exposures which consist of therapeutic error, misuse, general, and unknown. Therefore, abuse and therapeutic errors can not represent intentional and unintentional exposures, which are the outcomes defined in the study synopsis. If the other cases (misuse, suspected suicide, general, and unknown) are not of interest, the sponsor should modify the goals and outcomes in the Study 3 synopsis.*

The units of the adjusted rates are inconsistent for Study 3. The population adjusted rates were reported both per 1,000,000 population and per 100,000 population; the URDD adjusted rates were reported both per 10,000 URDD and per 1,000 URDD. Consistent units should be used in the report to avoid confusion.

The mortality defined in the Study 3 synopsis and the street prices defined in the Study 5 synopsis were not included in the report.

In Study 3, for the population-adjusted exposure rate, the denominator population was estimated from the 2000 and 2010 US Census by linear interpolation adjusting for 0.24% population growth each quarter [9.7%/(10 years X 4 quarters)]. For the URDD-adjusted exposure rate, the denominator URDD was purchased from SDI Health and IMS Health, representing the number of unique individuals who filled a prescription at pharmacies for a particular product within a quarter.

Reviewer Comments:
The reported numbers of abuse and drug diversion for OxyContin during the post-ORF period include events for both original and reformulated OxyContin. Therefore, the actual effect of ORF was not properly estimated because the reported abuse and drug diversion rates after the introduction of ORF estimated the combined effects for original and reformulated OxyContin.

The derivation of the population-adjusted rates in Study 3 and 5 are problematic. Based on the "Covered population" and "Percent of Population covered" in the Table 28 of the

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[2] NDA 022272 OxyContin (oxycodone hydrochloride) Controlled-Release Tablets, Post-marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death, submitted to DARRTS on January 26, 2011 for NDA #022272 (protocol).

Study 3 report, the US population for each quarter can be derived (see Table 2). The derived US population does not increase by 0.24% each quarter. We do not know how the population growth rate 0.24% per quarter impacts the calculation of covered population in the report.

In addition, the sponsor did not provide information on how the percent of population covered in RADARS Poison Center Program was estimated for each quarter. The percent of coverage was relatively stable in the pre-ORF period (b) (4) *from 2008-Q4 to 2010-Q3), and increased in the post-ORF period (* (b) (4) *from 2010-Q4 to 2012-Q1). The inflation of the covered US population in the RADARS Poison Center Program will lead to a smaller population-adjusted rate given the same number of events.*

Similarly, we derived the US population for Study 5 (see Table 3). Since Study 5 did not include any information for the adjusted population, we cannot understand how the US population was estimated and why it fluctuated from 2008-Q4 to 2012-Q1. Furthermore, the sponsor did not clarify why the percent of population covered in RADAS Drug Diversion Program went up and down from 2008 to 2012. The percentages were ranged from (b) (4) *in the pre-ORF period and from* (b) (4) *in the post-ORF period.*

The denominator of population-adjusted rates was the covered population in the RADARS Poison Center Program or Drug Diversion (DD) Program. This adjusted population is more related to the total US population. Note that the adjusted population is not the population who used OxyContin. In contrast, the URDD population is more related to the drug dispensed considering that the drug use pattern may change over time. For instance, if less people among the US population used OxyContin after the introduction of ORF, the population-adjusted rates in the report would underestimate the abuse rate for OxyContin. In such case, the URDD-adjusted rates will reflect the abuse rate for the actual OxyContin dispensing and are more interpretable to the effect of ORF.

Table 2: Covered population and derived US population for Study 3 (RADARS-Poison Centers)

	Covered Population in RADARS Poison Center Program	Percent of Population Covered	*Derived US Population*
2008-Q4			(b) (4)
2009-Q1			
2009-Q2			
2009-Q3			
2009-Q4			
2010-Q1			
2010-Q2			
2010-Q3			
2010-Q4			
2011-Q1			
2011-Q2			
2011-Q3			
2011-Q4			
2012-Q1			

Table 3: Covered population and derived US population for Study 5 (RADARS-Drug Diversion)

	Covered Population in RADARS Drug Diversion Program	Percent of Population Covered	*Derived US Population*
2008-Q4			(b) (4)
2009-Q1			
2009-Q2			
2009-Q3			
2009-Q4			
2010-Q1			
2010-Q2			
2010-Q3			
2010-Q4			
2011-Q1			
2011-Q2			
2011-Q3			
2011-Q4			
2012-Q1			

3.1.2 Statistical Methods

Study 3 tested two hypotheses about the impact of ORF following its introduction: (1) if the rates of mentioning OxyContin among poison center abuse exposures cases decline; and (2) if the rates of mentioning OxyContin among poison center therapeutic error cases decline.

Study 5 considered two hypotheses about the impact of ORF following its introduction: (1) if the rates of drug diversion mentioning OxyContin declines; and (2) if the decline for OxyContin is greater than changes observed in other prescription opiods and IR oxycodone.

Although Poisson interrupted time series were proposed for Study 3 and 5 in the protocol, in the report, negative binomial regression models were fit using the log of denominator (population and URDD) as the offset variable for each outcome of interest (abuse exposure rates, therapeutic error exposure rates, and diversion rates). For each outcome, the sponsor tested for differences in the mean level before and after introduction of ORF for each of the two drug groups (OxyContin vs. other opioids). An interaction term was included to test if the declines observed for OxyContin were different (in particular, greater) than those observed for other opioids. Because of the low number of data points and the adjustment for over dispersion in the negative binomial regression model, the results represented in the report do not incorporate a correction for serial correlation. The sponsor claimed that their sensitivity analyses suggest that the interpretations are robust to the inclusion of an autoregressive correlation structure, without showing the sensitivity analyses results in the report.

Following this analysis, these negative binomial models were fit comparing each of the six post-ORF introduction quarters to the average pre-ORF rate. The average pre-ORF rate used in the comparison was calculated by averaging four quarters data before ORF introduction (2009-Q3, 2009-Q4, 2010-Q1, and 2010-Q2).

Reviewer Comments:
In the protocol, Poisson regression models with AR(1) autocorrelation were proposed. Poisson regression makes an assumption that the variance of counts within covariate group is equal to the mean. Negative binomial regression model relaxes this assumption by introducing an additional parameter that allows for greater variance.

Negative binomial regression model is acceptable if there is not convergence problem in parameter estimations. However, due to the limited number of data points available in these studies, convergence could be problematic and this may lead to biased estimate of parameters.

The sponsor did not provide sufficient information in term of the models and their corresponding hypothesis tests in the protocol and report. Without a clear understanding of the model fitting, statistical reviewer is not able to provide further comments on the analysis result.

We recommend the sponsor should explicitly write out the negative binomial regression model equations for each hypothesis test and clarify how the model was fit to compare the rate for each of the six post-ORF introduction quarters to the average pre-ORF rate. Additionally, the sponsor should specify how the issue of multiple comparisons was handled in the model.

3.1.3 Sponsor's Results and Reviewer's Comments

Abuse, unintentional therapeutic errors, and diversions for OxyContin and other opioids were shown in Table 28 and 33 in the sponsor's report. For all three outcomes, the numbers of events for OxyContin declined from the pre-ORF period to post-ORF period. The numbers of events for other prescription opioids was relatively stable or increased.

Based on the negative binomial regression, the average post-ORF URDD-adjusted abuse rates and URDD-adjusted therapeutic error rates for OxyContin and other prescription opioids were lower than the corresponding average pre-ORF rates. Based on the negative binomial regression, the decrease in URDD-adjusted abuse rates for OxyContin is larger than that for other prescription opioids. However, the decrease in the URDD-adjusted therapeutic error rates was similar for OxyContin and other prescription opioids (see Figure 24 and 25 in the sponsor's report).

Reviewer Comments:
Without sufficient description on the model fitting and hypothesis testing, statistical reviewer is not able to provide comments on the analysis results for URDD-adjusted abuse rates.

3.1.4 Summary

Study 3 and Study 5 were designed to assess abuse, therapeutic errors, and drug diversion of OxyContin and other opioids before and after the introduction of ORF through the RADAS System. The numbers of cases, the population-adjusted rates, and the URDD-adjusted rates of OxyContin and other opioids were reported by quarters from 2008Q4 to 2012 Q1. Negative binomial regression models were used to evaluate if the abuse rates and therapeutic error rates for OxyContin declined after the introduction of ORF.

The following issues were found in the report for Study 3 and 5:

1. Limited data points available after the introduction of ORF up to the date of the report.
2. The population-adjusted rates for each outcome are unreliable due to the problematic derivation of covered population in the report. The sponsor did not clarify how the covered populations and percentage of populations covered in RADARS System were estimated, and how to connect the covered population to the population who used OxyContin.

3. The sponsor did not provide sufficient information in term of the models and their corresponding hypothesis tests in the protocol and report. Without a clear understanding of the model fitting, statistical reviewer is not able to provide further comments on the analysis result.
4. The sponsor did not clarify if multiplicity adjustment of type I error were used for multiple tests.
5. Results on mortality and street prices are missing from the study report.
6. The units of adjusted rates are not inconsistent.

3.2 Study 4 (National Surveys)

3.2.1 Outcomes

The primary outcome for Study 4 is the non-medical use of OxyContin, IR oxycodone, and other prescription opioids. The measures were obtained from three surveys: the National Survey on Drug Use and Health (HSDUH), the Monitoring the Future Study (MTF), and the RADARS System College Survey.

Reviewer's Comments:
NSDUH is a reliable data source that provides annual national non-medical use of pharmaceutical drugs for children and adults (12+ years old). However, data covering post-ORF period is not available from NSDUH. MTF is an ongoing study that focuses on secondary school students, college students, and young adults. The sponsor found that annual prevalence trends of use of OxyContin, marijuana, and cocaine were generally greater in MTF than that in NSDUH[3]*. This discrepancy is consistent over the five year time span. The discrepancy may be due to the different questions presented in the two surveys and the misclassification in the reporting. Given the consistent discrepancy observed, the validity of MTF survey is questionable.*

3.2.2 Statistical Methods

Study 4 tested the hypothesis whether the change from the average percent of respondents reporting use of OxyContin before introduction of ORF to the quarterly percent of respondents reporting OxyContin following introduction of ORF differed from the corresponding changes observed for IR oxycodone and other opioids. Negative binomial regression model was used to compare endorsement rates by time and by drug group from 2009-Q3 to 2011Q4.

Reviewer Comments:
The sponsor did not provide sufficient information in term of the models and their corresponding hypothesis tests in the protocol and report. Without a clear understanding of the model fitting, statistical reviewer is not able to provide further comments on the analysis method.

[3] See Page 93-94 in the sponsor's report.

3.2.3 Sponsor's Results and Reviewer's Comments

Based on the negative binomial regression, data from the RADARS College Survey shows no significant change in prevalence of nonmedical OxyContin use after the introduction of ORF, and no significant difference on change among drug groups.

Reviewer Comments:
Without the explicit description of the statistical method (negative binomial regression model), statistical reviewer is not able to provide further comments on the analysis result.

3.2.4 Summary

Study 4 was designed to examine the trends of non-medical use of OxyContin and other opioids before and after the introduction of ORF. In the RADARS College Survey, no significant change was found in prevalence of nonmedical OxyContin use after the introduction of the ORF, and no significant difference on the change by drug groups. Data covering the post-ORF period is not available from NSDUH. Consistent discrepancy was found over the five years span for NSDUH and MTF in this study. Given the consistent discrepancy observed, the validity of MTF survey is questionable.

The following issues were found in the report for Study 4:

1. Limited data points available after the introduction of ORF up to the date of the report.
2. Data source may not be reliable given the consistent discrepancy observed on prevalence trends among different surveys.
3. No adjusted prevalence was reported.
4. Without explicit description of the statistical method (negative binomial regression model) in the report, statistic review is unable to evaluate the results.
5. The sponsor did not clarify if multiplicity adjustment of type I error were used for multiple comparisons.

3.3 Study 11 (National Poison Data System)

3.3.1 Outcomes

The outcomes were defined as intentional abuse, unintentional therapeutic errors, and unintentional general exposures for OxyContin, heroin, and SE oxycodone (excluding OxyContin). Two adjusted rates were reported: the number of exposures per 100,000 population and the number of exposures per 100 prescriptions.

In Study 5, for the population-adjusted exposure rate, the denominator, the population by quarter, was obtained from Moody's analytical estimates (2009-11). For the prescription-adjusted exposure rate, the denominator, the number of prescriptions by quarter was obtained from the IMS (previously SDI) VONA prescription data system. Exposures per 100 prescriptions were not calculable for heroin because it is not prescribed.

Reviewer Comments:
As addressed in the review of Study 3 and 5, since the population estimates are for the total US population and not for the population actually used the drug, the population-adjusted rates do not reflect the abuse rates for the actual drug dispensing. The prescription-adjusted rates may be more interpretable to assess the effect of ORF.

3.3.2 Statistical Methods

All measures were descriptively shown in tables or figures. No statistical tests were conducted in the report.

Reviewer's Comments
Only descriptive statistics were reported. The sponsor should conduct more formal statistical testing.

3.3.3 Sponsor's Results and Reviewer's Comments

The relative change from baseline (i.e. the average from 2009Q3 to 2010Q2) for the number of intentional abuse and therapeutic errors, and for the corresponding adjusted rates for OxyContin and other oxycodone products were shown in Figure 60 and 61 in the sponsor's report.

The numbers of abuse and therapeutic errors exposures for OxyContin declined and the corresponding numbers for other oxycodone products increased in the post-ORF period. The population adjusted exposures were similar as the number of exposures. This implies that the adjustment for population covered for National Poison Data System is not informative since the population covered is close to a constant, except for the approximately 0.9% increase in population size per year.

After adjusted by the number of prescriptions, the abuse for OxyContin declined in the post-ORF period, but the magnitude of the decline is much smaller than the non-adjusted abuse exposure; and the therapeutic errors for OxyContin in the post-ORF period were generally the same as the baseline exposure. No increase was found in the corresponding prescription-adjusted exposures for other opioids in the post-ORF period.

Reviewer Comments:
As previously addressed, the discrepancy in the trends shown by population-adjusted exposures (similar as the number of exposures in this study) and prescription-adjusted exposures indicates that the latter accounted for changes in the actual drug dispensing and is more relevant to assess the effect of ORF.

3.3.4 Summary

Study 11 focused on abuse, therapeutic errors of OxyContin and other opioids before and after the introduction of ORF through the National Poison Data System. Different trends for the change of outcomes were shown by using the number of exposures (similar as the population-adjusted exposures) and prescription-adjusted exposures.

The following issues were found in the report for Study 11:

1. Limited data points available after the introduction of ORF up to the date of report.
2. Only descriptive statistics were shown in the report. The sponsor should conduct more formal statistical testing.

4. SUMMARY AND RECOMMENDATIONS

The four post-marketing observational studies were designed to assess the effect of reformulated OxyContin on abuse with different outcomes and data sources. The basic design for these studies is to assess changes from before to after the introduction of ORF, and compare changes for OxyContin to changes for comparator opioids. Various outcomes on abuse and diversion from different data sources were reported for OxyContin and comparator opioids by quarter from 2008Q4 to 2011Q4 or 2012Q1 depending on the data source. Negative binomial regression was used to evaluate the effect of ORF. However, no sufficient information on the models and the corresponding hypothesis tests were provided in the report. Therefore, the statistical approach and results cannot be fully evaluated.

Several limitations were found in these studies. First, in all studies, the reported numbers of abuse and drug diversion for OxyContin during the post-ORF period include events for both original and reformulated OxyContin. Therefore, the actual effect of ORF was not properly estimated because the reported abuse and drug diversion rates after the introduction of ORF estimated the combined effects for original and reformulated OxyContin. Other limitations include the potential under-reporting and misclassification biases for the outcomes in the surveillance system and self-reported surveys.

Finally, in order to properly characterize the abuse pattern over time, we need ensure that the trend is stable and well characterized and to consider the autocorrelation structure and possible periodical or seasonal patterns in the data. The accuracy, in terms of bias and variability, of the outcome measure would also affect the length of the necessary observational period. The four studies covered in this review had only 1 to 1.5 years of data after ORF was introduced into the market, i.e., 5-6 data points. The adequacy of data points/structure for these studies should be further evaluated upon the completion of the study. Therefore, the results presented in this preliminary study report do not provide conclusive evidence for the evaluation of abuse deterrence.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

IND/Study Name:	029038/OTR1018
Drug Name:	Oxycodone HCl Tamper Resistant Controlled-Release (OTR)
Indication(s):	Moderate to severe pain
Applicant:	Purdue Pharma, L. P.
Date(s):	Consult received: 06/29/2012 Completion date: 08/20/ 2012
Review Priority:	S
Biometrics Division:	DB VI
Statistical Reviewer:	Ling Chen, Ph.D., Expert Mathematical Statistician, Special Project Team.
Concurring Reviewers:	Stella Machado, Ph.D., Division Director, Acting Team Leader
Medical Division:	Controlled Substance Staff
The CSS Team:	James Tolliver, Ph.D., Pharmacologist, OD/CSS Silvia Calderon, Ph.D., Pharmacology Team Leader
Project Manager:	Sandra Saltz, OD/CSS

Keywords: Crossover design; Drug abuse potential study; Self-reported endpoint; Multiple endpoints

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1. Executive Summary

Study OTR1018 was a randomized, double-blind, placebo and positive controlled crossover study. There were five treatments in the study. They were

1. OTRC: 30 mg coarsely crushed OTR tablets (Oxycodone HCl OTR tablets, Purdue Pharma, L.P.)
2. OTRF: 30 mg finely crushed OTR tablets (Oxycodone HCl OTR tablets, Purdue Pharma, L.P.)
3. OCF: 30 mg finely crushed OC tablets (OxyContin® tablets, Purdue Pharma, L.P.)
4. Oxy API: 30 mg Oxy API powder (Oxycodone HCl USP powder, (b) (4))
5. Placebo: finely crushed OC placebo (Placebo for OxyContin® 30mg tablets, Purdue Pharma, L.P.)

All treatments in the study were administered intranasally.

This review was to assess one of the objectives of the study. That is to evaluate intranasal abuse potential and pharmacodynamic (PD) effects of coarsely and finely crushed Oxycodone Tamper Resistant tablets (OTR) compared to finely crushed OxyContin® (OC), oxycodone active pharmaceutical ingredient (Oxy API), and OC placebo in healthy, adult recreational opioid users with a history of intranasal drug abuse.

The reviewer first used conventional assessment methods to compare the mean (or median) responses to OTR coarsely crushed or finely crushed to those of finely crushed OC and Oxy API powder for Drug Liking VAS, Overall Drug Liking VAS, ARCI MBG and High VAS. The analysis results showed that the mean (or median) responses to OC finely crushed and Oxy API powder were significantly greater than those to OTR finely or coarsely crushed except in comparison between OTR finely crushed and OC finely crushed (and Oxy ARP powder) for ARCI MBG.

The reviewer also used heat maps to display the individual subject responses, as well as calculated percent reduction for OTR relative to OC and Oxy API.

The heat maps for Drug Liking VAS showed that overall the time course response profiles for individual subjects to OTRF and OTRC were very different from those to OC Fine and Oxy API. Given score liking in Emax greater than 80 for the positive control drugs, approximately 29.2% (7/24) and 9.1% (2/22) of subjects had at least 50% reduction for OTRF relative to OCF and Oxy API, respectively, and approximately 58.3% (14/24) and 50% (11/22) of subjects had at least 50% reduction for OTRC relative to OCF and Oxy API, respectively.

Even though there were still some subjects who strongly liked OTR (finely crushed or coarsely crushed) administered intranasally, the study clearly showed that the OTR formulation may have the advantage of making some subjects dislike or less like the drug through nasal route, especially, for coarsely crushed OTR tablets.

2. Overview Study OTR 1018

Study OTR1018 was a single-center, double-blind study in recreational opioid users to evaluate the abuse potential, pharmacokinetics, and safety of crushed and intranasally administered oxycodone HCl tamper resistant tablets.

2.1 Objectives of the study

Objectives of the study are:

- to evaluate intranasal abuse potential and pharmacodynamic (PD) effects of coarsely and finely crushed Oxycodone Tamper Resistant tablets (OTR) compared to finely crushed OxyContin® (OC), oxycodone active pharmaceutical ingredient (Oxy API), and OC placebo in healthy, adult recreational opioid users with a history of intranasal abuse;
- to evaluate the safety and tolerability of intranasally administered crushed OTR in healthy, adult recreational opioid users with a history of intranasal abuse; and
- to determine the comparative pharmacokinetics of intranasally administered crushed OTR compared to OC and Oxy API.

Reviewer's comment: This review report is for the first study objective.

2.2 Study design

The study consisted of four phases:

Screening Phase: Visit 1 for inclusion/exclusion screening and Visit 2 for a Naloxone Challenge to screen for symptoms of opiate withdrawal

Qualification Phase: Visit 3 for a randomized, crossover pharmacologic qualification (30 mg Oxy API powder and lactose powder placebo) to ensure tolerability and appropriate reporting of positive subjective effects

Treatment Phase: Visit 4 to Visit 8 where each of the following singe-dose treatments were administered (one per visit): 30 mg coarsely crushed OTR tablets, 30 mg finely crushed OTR tablets, 30 mg finely crushed OC tablets, 30 mg Oxy API powder, and finely crushed OC placebo

Follow-up: Visit 9 for a safety follow-up, 2 to 4 days after the last Treatment Visit drug administration

Two 5x5 Williams squares were used for the sequences in the treatment phase. Subjects were randomly assigned to one of the ten sequences. The washout period between two treatments was generally 7 days and no less than 2 days.

2.3 Treatment notations

There were five treatments in the Treatment Phase. These treatments are

6. OTRC: 30 mg coarsely crushed OTR tablets (Oxycodone HCl OTR tablets, Purdue Pharma, L.P.)
7. OTRF: 30 mg finely crushed OTR tablets (Oxycodone HCl OTR tablets, Purdue Pharma, L.P.)
8. OCF: 30 mg finely crushed OC tablets (OxyContin® tablets, Purdue Pharma, L.P.)
9. Oxy API: 30 mg Oxy API powder (Oxycodone HCl USP powder, (b) (4))
10. Placebo: finely crushed OC placebo (Placebo for OxyContin® 30mg tablets, Purdue Pharma, L.P.)

2.4 Abuse Potential Measures

The primary measures consisted of the visual analog scales (VAS) for Drug Liking ("at this moment") and Overall Drug Liking, Subjective Drug Value, and Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG) scale.

Secondary measures were included to evaluate other subjective effects including balance of effects (Take Drug Again VAS); positive effects (High VAS and Good Effects VAS); negative effects (Bad Effects VAS, ARCI Lysergic Acid Diethylamide [LSD], and Subject-rated Assessment of Intranasal Irritation [SRAII]); sedative effects (ARCI Pentobarbital and Chlorpromazine Alcohol Group [PCAG] and Alertness/Drowsiness VAS); and other drug effects (Any Drug Effects VAS). Observer-related Assessment of Intranasal Irritation (ORAII) using endoscopy was also conducted as was the objective measure of pupillometry.

2.5 Number of Subjects

Thirty subjects were randomized to the Treatment Phase, and 27 subjects completed all 5 Treatment Visits.

2.6 Statistical Methodologies Used in the Sponsor's Analyses

Pharmacodynamic data at each time point were summarized by descriptive statistics and presented graphically (where appropriate) for the Pharmacodynamic Population for the Treatment Phase; the primary measures, pertinent to qualification, were also summarized for the Qualification Phase. Derived parameters were summarized using descriptive statistics and boxplots. Pharmacodynamic parameters (Emax, Emin, and/or Time Weighted mean (TWmean), as appropriate) were analyzed using a mixed-effect model for a crossover study. The model included treatment, period, sequence, and first-order carryover effect as fixed effects, baseline (pre-dose) measurement as covariate where applicable, and subject nested within treatment sequence as random effect. A washout of at least 3 days was used in order to minimize the potential for carryover effects. If the carryover effect was found to be non-significant at the 25% level, then the term was dropped from the analysis model. Baseline and carryover were included as applicable. Least square means, standard errors (SE) and 95% two-sided confidence intervals for treatments and treatment differences were derived from the mixed-effects model. P values were provided for the effects and the contrasts. The contrasts were presented only if there was an overall treatment effect.

Reviewer's comments: The Sponsor mentioned a washout of at least 3 days. This is different from in other place of the study report where the Sponsor reported that a washout period was generally 7 days, but no less than 2 days.

In addition, the Sponsor did not provide statistical methodology for the cases when the model assumptions are not satisfied. It seems that the Sponsor did not check the model assumptions in their analysis.

2.7 Sponsor's results and conclusion

The Sponsor summarized their PD study results as follows:

- Intranasal administration of both positive controls, OC and Oxy API, resulted in significant increases in Emax for the primary measures of Drug Liking VAS, Overall Drug Liking VAS, Subjective Drug Value and ARCI MBG compared to placebo, thereby confirming validity of the study.
- Consistent with results of the primary measures, intranasal administration of OC and Oxy API resulted in statistically significant changes from placebo on the secondary measures of balance (Take Drug Again), positive effects (Good Effects, High VAS), sedative effects (Alertness/Drowsiness VAS, ARCI PCAG), any effects, and pupillometry.
- Intranasal administration of OTRF and OTRC induced response patterns on the primary measures that, in general, were greater in magnitude than those of placebo, but were significantly lower than those of OC and Oxy API. A similar pattern was observed on the secondary measures.
- In addition to being significantly lower, peak effects for subjective measures and pupillometry occurred later for OTR (typically 1 to 2 hours post-dose) compared with OC and Oxy API (typically 0.5 hours post-dose).
- Of note, the variability of the derived parameters was observed to be higher for the OTR treatments, OTRC in particular, compared with OC and Oxy API.
- Consistent with the known abuse liability of oxycodone, none of the active treatments was associated with prominent negative subjective drug effects (as measured using Bad Effects VAS, ARCI LSD); however, OTR was associated with higher Emax on subject- and observer-rated measures of intranasal irritation (need to blow nose; nasal congestion) compared to OC and Oxy API, indicating greater nasal irritation with OTR.

The sponsor concluded that

The current abuse potential study was conducted to investigate the subjective and objective effects of OTR in comparison with crushed OC, Oxy API, and placebo when administered intranasally in recreational opioid users with a history of intranasal drug abuse/misuse. Based on the overall pattern of response on the measures evaluated in this study, it is evident that intranasally administered OTR, whether fine or coarse crushed, produces subjective and objective effects of smaller magnitude and are delayed compared with those of intranasally administered OC and Oxy API. In addition to reduced positive subjective effects, OTR is more likely to be associated with intranasal irritation compared to the 2 positive controls. Therefore, it can be concluded that OTR has less potential for intranasal abuse compared to OC and Oxy API.

3. Data location

The following was the link of the data sets used in this review.

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4. Reviewer's analysis

This reviewer evaluated the sponsor's claim in several ways and focused on the primary measures Drug Liking VAS, Overall Drug Liking VAS, and ARCI MBG as well as High VAS. The evaluation of deterrent effects for OTR relative to OC and Oxy API was based on Drug Liking VAS.

4.1 Conventional analysis

The primary endpoint was Emax (maximum PD response) for each abuse potential measure. If predose response was collected, Emax was calculated based on change from predose responses.

Table 1 summarizes the mean, standard deviation, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for Emax of Drug Liking VAS, Overall Drug Liking VAS, High VAS, and ARCI MBG.

Table 1: Summary Statistics for Three Primary Measures and High VAS

Abuse Potential Measure	TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
Drug Liking VAS	OCF	27	93.78	2.76	51	99	100	100	100
	OTRC	27	71.70	4.28	16	51	68	100	100
	OTRF	27	79.33	4.08	36	51	87	100	100
	Oxy API	27	88.56	3.27	50	81	100	100	100
	Placebo	27	52.26	2.45	0	51	51	52	80
Overall Drug Liking VAS	OCF	27	86.96	4.34	8	83	100	100	100
	OTRC	27	59.63	4.84	0	50	51	88	100
	OTRF	27	67.78	5.70	0	50	73	98	100
	Oxy API	27	83.93	3.73	50	64	95	100	100
	Placebo	27	50.63	2.32	0	50	51	51	83
High VAS*	OCF	27	92.15	3.26	49	95	100	100	100
	OTRC	27	59.74	6.34	0	50	65	85	100
	OTRF	27	73.11	6.72	0	60	84	100	100
	Oxy API	27	87.52	4.33	25	83	100	100	100
	Placebo	27	23.74	5.86	0	0	3	50	100
ARCI MBG*	OCF	27	6.07	1.04	0	1	5	10	16
	OTRC	27	3.59	1.07	-1	0	1	5	16
	OTRF	27	4.33	1.02	0	0	2	6	16
	Oxy API	27	5.74	1.01	0	1	4	11	16
	Placebo	27	1.26	0.61	-1	0	0	1	16

*: Emax was calculated based on change from predose response.

The statistical model used in the reviewer's analysis was the mixed-effect model with sequence, treatment, and period as fixed effects, and subject nested within sequence as a random effect. If

the model assumptions were not satisfied, the Wilcoxon sign-rank test on the within-subject differences was used.

Table 2 presents the results from statistical analysis for Drug Liking VAS and Overall Drug Liking VAS based on Wilcoxon sign-rank test. The first quartile (25th percentile), median, and the third quartile (75th percentile) are also listed in the table with the original scale.

Table 2: Statistics Test Results for Comparisons in Medians

Comparison	Drug Liking VAS				Overall Drug Liking VAS			
	Q1	Med	Q3	P-value	Q1	Med	Q3	P-value
OCF - P	37	49	49	<0.0001	26	45	49	<0.0001
Oxy API - P	27	38	49	<0.0001	11	42	50	<0.0001
OTRF - P	1	27	48	<0.0001	0	22	48	0.0113
OTRC - P	0	18	48	0.0003	-7	1	38	0.1213
OCF - Oxy API	0	0	4	0.0498	-2	0	7	0.4373
OCF - OTRF	0	8	30	0.0002	0	9	49	0.0017
OCF - OTRC	0	27	38	0.0002	3	33	50	0.0006
Oxy API - OTRF	0	3	18	0.0082	0	8	31	0.0003
Oxy API - OTRC	0	12	36	0.0004	0	26	45	0.0001
OTRF - OTRC	0	0	21	0.1108	0	6	35	0.0426

Table 2 shows that

- The medians of OCF, Oxy APl, OTRF and OTRC were larger than that of placebo for both Drug Liking VAS and Overall Drug Liking VAS. These differences are statistically significant except the comparison between OTRC and Placebo for Overall Drug Liking VAS.
- There was zero difference in medians between OCF and Oxy API for both Drug Liking VAS and Overall Drug Liking VAS. However, based on the Wilcoxon sign-rank test, the median of OCF was significantly larger than that of Oxy API.
- Medians of OCF and Oxy API are significantly greater than those of OTRF and OTRC.
- The differences in medians between OTRF and OTRC were zero for Drug Liking VAS. But the median of OTRF was significantly larger than that of OTRC for Overall Drug Liking VAS.

Statistical test results for High VAS and ARCI MBG are presented in Table 3.

From Table 3, one may see that

- The means of OCF, Oxy APl, OTRF and OTRC were significantly larger than those of placebo for both High VAS and ARCI MBG.
- There were no significant differences in means between OCF and Oxy API for both High VAS and ARCI MBG.

Table 3: Statistical Test Results (p-values) for Comparisons in Means

Comparison	High VAS				ARCI MBG			
	Lsmean	Diff	StdErr	P-value	Lsmean	Diff	StdErr	P-value
OCF - P	91.87	67.51	6.60	<0.0001	5.87	4.72	0.87	<0.0001
	24.36				1.15			
Oxy API - P	86.54	62.51	6.76	<0.0001	5.66	4.51	0.89	<0.0001
	24.36				1.15			
OTRF - P	72.85	48.50	6.57	<0.0001	4.21	3.07	0.87	0.0006
	24.36				1.15			
OTRC - P	59.25	34.89	6.59	<0.0001	3.42	2.27	0.87	0.0102
	24.36				1.15			
OCF - Oxy API	91.87	5.33	6.60	0.4212	5.87	0.21	0.87	0.8120
	86.54				5.66			
OCF - OTRF	91.87	19.02	6.55	0.0045	5.87	1.66	0.86	0.0576
	72.85				4.21			
OCF - OTRC	91.87	32.62	6.54	<0.0001	5.87	2.45	0.86	0.0054
	59.25				3.42			
Oxy API - OTRF	86.54	13.69	6.63	0.0413	5.66	1.45	0.87	0.1001
	72.85				4.21			
Oxy API - OTRC	86.54	27.29	6.61	<0.0001	5.66	2.24	0.87	0.0115
	59.25				3.42			
OTRF - OTRC	72.85	13.61	6.54	0.0399	4.21	0.79	0.86	0.3606
	59.25				3.42			

- There were no significant difference in means between OTRF and both OCF and Oxy API for ARCI MBG. But significant results were found for OTRC when compared to OCF and Oxy for the same measure.
- For High VAS OCF and Oxy API had significantly higher means compared to both OTRF and OTRC.
- OTRF had significantly greater mean than OTRC for High VAS, but no significant difference in means was found between OTRF and OTRC for ARCI MBG.

4.2 Comparison of Deterrent Effects for OTRC and OTRF to OCF and Oxy API on Drug Liking VAS (bipolar)

4.2.1 Descriptive Statistics

Table 4 summarizes the mean, standard deviation, minimum, the first quartile (Q_1), median, the third quartile (Q_3), and maximum for Emax of Drug Liking VAS.

Table 4: Summary Statistics for Emax of Drug Liking VAS

TRT	N	Mean	StdErr	Min	Q1	Med	Q3	Max
OCF	27	93.78	2.76	51	99	100	100	100
OTRC	27	71.70	4.28	16	51	68	100	100
OTRF	27	79.33	4.08	36	51	87	100	100
Oxy API	27	88.56	3.27	50	81	100	100	100
Placebo	27	52.26	2.45	0	51	51	52	80

Table 4 shows that for Emax of Drug Liking VAS, OTRF and OTRC had medians 87 and 68, respectively, while the medians of both OCF and Oxy API were 100. Approximately 25% of subjects who were administered OTRC or OTRF intranasally had an Emax 51 or less for liking, while the 25th percentiles for OCF and Oxy API were 99 and 81, respectively.

Figure 1 shows the mean time course profiles for Drug Liking VAS by treatment. The order of the profiles in the figure is as follows:

Placebo < OTRC < OTRF < Oxy API < OC Fine

at all time points except OTRF and OTRC at hour 6.

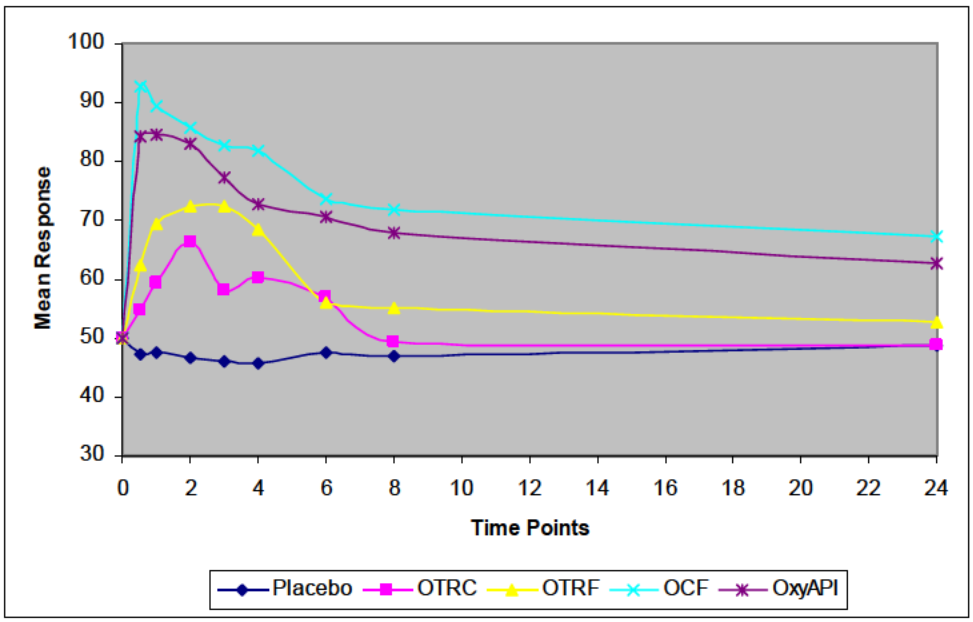

Figure 1: Mean Time Course Profiles for Drug Liking VAS (N=27)

OCF and Oxy API reached their peak mean responses at hour 0.5. OTRC and OTRF reached their peak mean response at hour 2. The mean responses of both OTRC and OTRF were around neutral after hour 6. However, the means of OCF at hour 6, 8 and 24 were 75, 72 and 67 respectively.

4.2.2 Heat map displays for Drug Liking VAS

Figure 2 shows Emax of Drug Liking from each subject by treatment. Remember that the statistical analysis was based on Emax in medians for this measure. One may see what the maximum response from each subject to each treatment was. In addition, one may visually compare the treatment differences. It can be noticed that some subjects had much lower Emax for OTR compared to OCF and Oxy API.

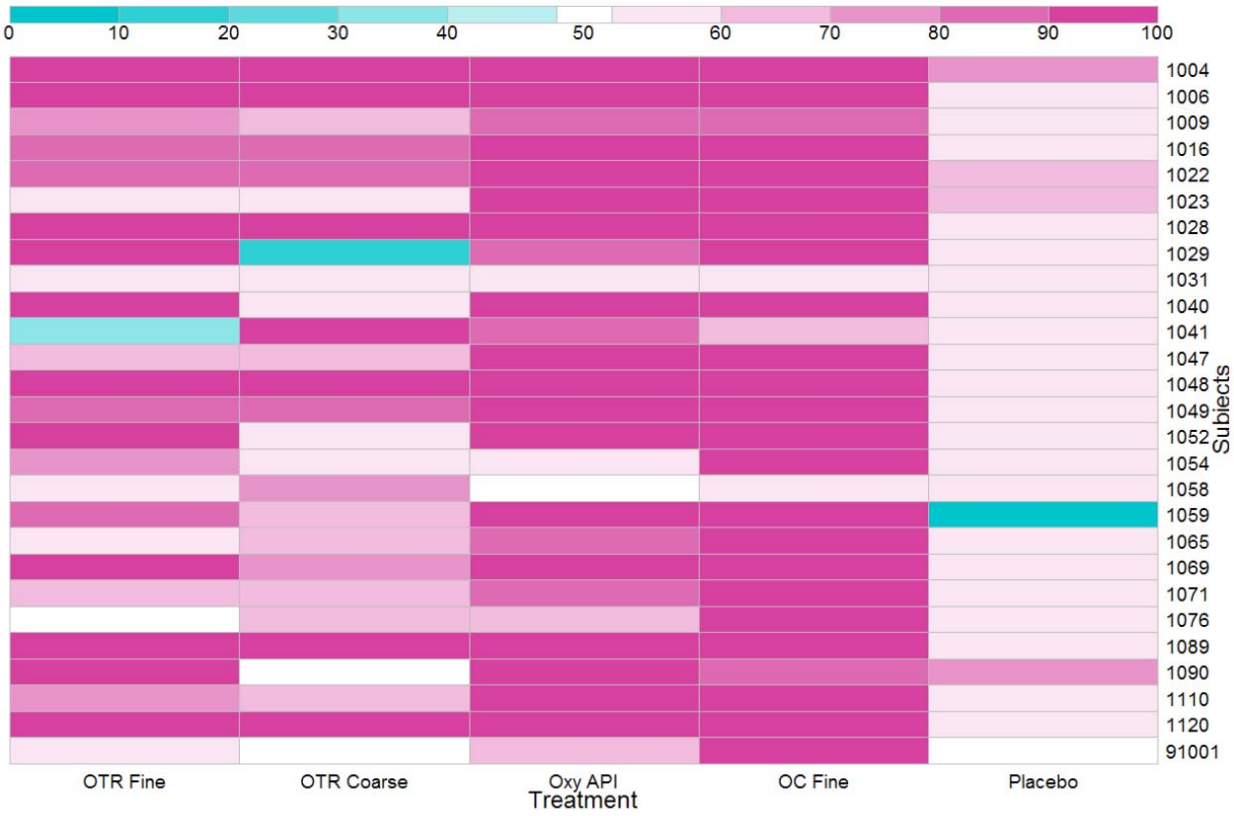

Figure 2: Emax of Drug Liking VAS by Treatment by Subject

Figure 3-7 show individual responses to each treatment overtime for Drug Liking VAS. From these graphs, one may see how an individual subject responded each treatment overtime; what time a subject reached his/her peak response; and how long the peak response lasted. Overall the time course response profiles for individual subjects to OTR are very different from those to OC Fine and Oxy API. One may also notice that subjects 1029 and 1059 disliked placebo for a long period of time. The reason why these subjects gave a strongly dislike score to placebo is unknown.

Figure 7: Individual Responses to Placebo for Drug Liking VAS

4.3 Percent reduction in Emax for the test drug relative to the positive control drugs for Drug Liking VAS

The following formula is used in calculation of the percent reduction.

$$\%\,reduction = \begin{cases} \dfrac{C-T}{C-50} \times \left(1 - \dfrac{P-50}{50}\right) \times 100\%, & if\ P > 55; \\ \dfrac{C-T}{C-50} \times 100\%, & if\ P \le 55. \end{cases}$$

where C, T and P denote the positive control drug, test drug and placebo respectively.

The term $1 - \frac{P-50}{50}$ is the penalty on the percent of reduction due to high placebo response, and is called *the adjustment factor for placebo*.

Tables 3-7 are the contingency tables of drug liking score in Emax to the positive control drug by percent reduction (%) for the following four comparisons.

1. OTRF versus OCF
2. OTRF versus Oxy API
3. OTRC versus OCF

4. OTRC versus Oxy API

Table 5: Contingency Table for C by Pct for Emax of Drug Liking VAS (OTRF vs. OCF)

C\Pct (%)	<0	0	(0, 10)	[10, 20)	(20,30]	[30,40)	[40,50)	[50,60)	(60,70]	[70,80)	[80, 90)	[90,100]	>100	Total
<=55		2												2
(55, 60]														
(60, 65]														
(65,70]													1	1
(70, 75]														
(75, 80]														
(80, 85]					1									1
(85, 90]	1													1
(90, 95]			1											1
(95,100]		8	1	2	1	1	1	2	1	1		3		21
Total	1	10	2	2	2	1	1	2	1	1		3	1	27
Pct (%)	4	37	7	7	7	4	4	7	4	4	0	11	4	100
Cpct (%)	100	97	60	52	45	37	34	30	23	19	15	15	4	

Note: 1. C, Pct, and Cpct denote response in Emax to the positive control drug, percentage of subjects, and cumulative percentage of subjects, respectively. 2. The cumulative percentages (Cpct) are not calculated based on the numbers from Percentage (Pct) in the table. They are rounded up based on the original values.

Table 6: Contingency Table for C by Pct for Emax of Drug Liking VAS (OTRF vs. Oxy API)

C\Pct (%)	<0	0	(0, 10)	[10, 20)	(20,30]	[30,40)	[40,50)	[50,60)	(60,70]	[70,80)	[80, 90)	[90,100]	>100	Total
<=55	2	1												3
(55, 60]														
(60, 65]												1		1
(65,70]												1		1
(70, 75]														
(75, 80]														
(80, 85]	1			1		1						1		4
(85, 90]													1	1
(90, 95]			1											1
(95,100]		9		2	1	1	1		1	1				16
Total	3	10	1	3	1	2	1		1	1		3	1	27
Pct (%)	11	37	4	11	4	7	4	0	4	4	0	11	4	100
Cpct (%)	100	89	52	48	37	33	26	22	22	19	15	15	4	

Note: 1. C, Pct, and Cpct denote response in Emax to the positive control drug, percentage of subjects, and cumulative percentage of subjects, respectively. 2. The cumulative percentages (Cpct) are not calculated based on the numbers from Percentage (Pct) in the table. They are rounded up based on the original values.

Table 7: Contingency Table for C by Pct for Emax of Drug Liking VAS (OTRC vs. OCF)

C\Pct (%)	<0	0	(0, 10)	[10, 20)	(20,30]	[30,40)	[40,50)	[50,60)	(60,70]	[70,80)	[80, 90)	[90,100]	>100	Total
<=55	1	1												2
(55, 60]														
(60, 65]														
(65,70]	1													1
(70, 75]														
(75, 80]														
(80, 85]							1							1
(85, 90]								1						1
(90, 95]			1											1
(95,100]		6		1	1			1	2	5	1	3	1	21
Total	2	7	1	1	1		1	2	2	5	1	3	1	27
Pct (%)	7	26	4	4	4	0	4	7	7	19	4	11	4	100
Cpct (%)	100	93	67	63	60	56	56	52	45	37	19	15	4	

Note: 1. C, Pct, and Cpct denote response in Emax to the positive control drug, percentage of subjects, and cumulative percentage of subjects, respectively. 2. The cumulative percentages (Cpct) are not calculated based on the numbers from Percentage (Pct) in the table. They are rounded up based on the original values.

Table 8: Contingency Table for C by Pct for Emax of Drug Liking VAS (OTRC vs. Oxy API)

C\Pct (%)	<0	0	(0, 10)	[10, 20)	(20,30]	[30,40)	[40,50)	[50,60)	(60,70]	[70,80)	[80, 90)	[90,100]	>100	Total
<=55	1	2												3
(55, 60]														
(60, 65]												1		1
(65,70]					1									1
(70, 75]														
(75, 80]														
(80, 85]						1	1	1					1	4
(85, 90]	1													1
(90, 95]			1											1
(95,100]		6		1	1			2	1	3	1	1		16
Total	2	8	1	1	2	1	1	3	1	3	1	2	1	27
Pct (%)	7	30	4	4	7	4	4	11	4	11	4	7	4	100
Cpct (%)	100	93	63	60	56	48	45	41	30	26	15	11	4	

Note: 1. C, Pct, and Cpct denote response in Emax to the positive control drug, percentage of subjects, and cumulative percentage of subjects, respectively. 2. The cumulative percentages (Cpct) are not calculated based on the numbers from Percentage (Pct) in the table. They are rounded up based on the original values.

Tables 5-8 give the following important information.

- The percentages of subjects who had Emax of Drug Liking VAS for OCF and Oxy API greater than 95 are approximately 77.8% (21/27) and 59.3 % (16/27), respectively.

- Given Emax of Drug Liking VAS greater than 95 for the positive control drugs, approximately 56.3% (9/16) and 38.1% (8/21) of subjects had no reduction for OTRF relative to OC Fine and Oxy API, respectively.
- Given Emax of Drug Liking VAS greater than 80 for the positive control drugs, approximately 29.2% (7/24) and 9.1% (2/22) of subjects had at least 50% reduction for OTRF relative to OC Fine and Oxy API, respectively.
- Overall approximately 37.0% (10/27) and 33.3% (9/27) of subjects had at least 30% reduction in Emax of liking for OTRF relative to OCF and Oxy API, respectively.
- Given Emax of Drug Liking VAS greater than 95 for the positive control drugs, approximately 28.6% (6/21) and 37.5% (6/16) of subjects had no reduction for OTRC relative to OCF and Oxy API, respectively.
- Given Emax of Drug Liking VAS greater than 80, approximately 58.3% (14/24) and 50% (11/22) of subjects had at least 50% reduction for OTRC relative to OCF and Oxy API, respectively.
- Overall approximately 55.6% (15/27) and 48.1% (13/27) of subjects had at least 30% reduction in Emax of liking for OTRC Fine relative to OC Fine and Oxy API, respectively.

Figure 8 shows the percent reduction profiles for Emax of Drug Liking VAS for the four comparisons.

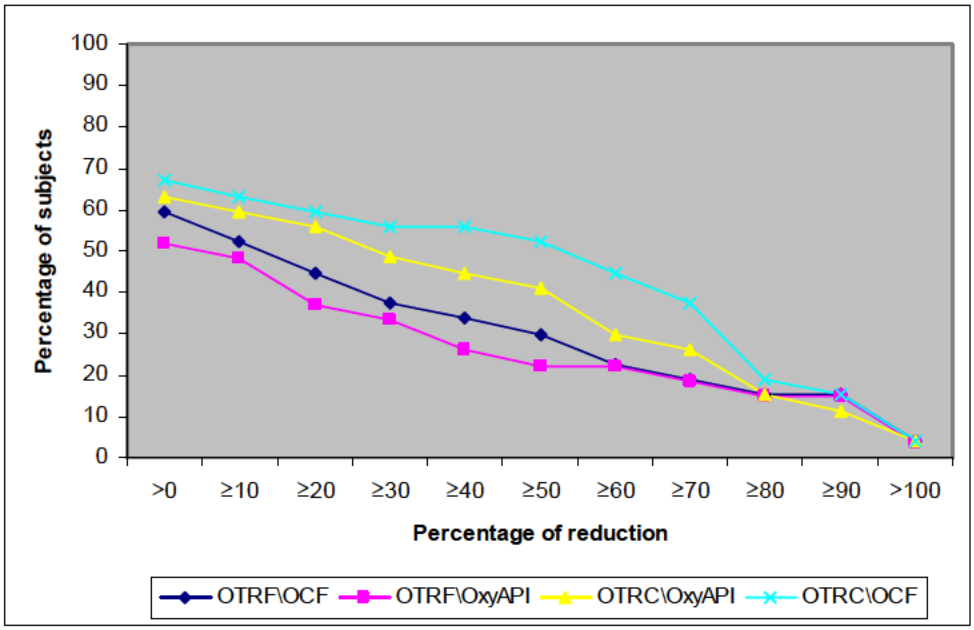

Figure 8 Percent Reduction Profiles for Emax of Drug Liking VAS

Figure 8 gives a picture of comparisons in percent reduction profiles. In four comparisons, the largest deduction is for OTRC relative to OCF.

5. Conclusion

The reviewer's statistical analysis showed that the median responses to OTRF and OTRC were significantly lower than those to OCF and Oxy API for Drug Liking VAS and Overall Drug Liking VAS. The heat maps for Drug Liking VAS showed that overall the time course response profiles for individual subjects to OTRF and OTRC were very different from those to OCF and Oxy API. Given Emax of Drug Liking VAS greater than 80 for the positive control drugs, approximately 29.2% (7/24) and 9.1% (2/22) of subjects had at least 50% reduction for OTRF relative to OCF and Oxy API, respectively, and approximately 58.3% (14/24) and 50% (11/22) of subjects had at least 50% reduction for OTRC relative to OCF and Oxy API, respectively.

Even though there were still some subjects who strongly liked OTR (finely crushed or coarsely crushed) administered intranasally in Study OTR1018, it is clear that the OTR formulation may have the advantage of making some subjects dislike or less like the drug through nasal route, especially, for coarsely crushed OTR tablets.

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/s/

LING CHEN
08/20/2012

STELLA G MACHADO
08/20/2012