CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272Orig1s014

OTHER REVIEW(S)

Labeling Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA#/ Supplement #	022272/S-014
Applicant Name	Purdue Pharma
Date of Submission	September 12, 2012
PDUFA Goal Date	April 14, 2012
Proprietary Name / Established (USAN) Name	OxyContin (Oxycodone Hydrochloride Controlled-Release) Tablets
Dosage Forms / Strength	Tablet
Proposed Indication(s)	For the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Introduction

This supplemental application proposes the addition of labeling language describing the results of pre- and post-marketing data from in vitro and in vivo abuse potential studies to the DRUG ABUSE AND DEPENDENCE section, (b) (4) The material intended to support of the proposed labeling changes were submitted in the NDA and to IND 029038. A review of the studies intended to support the labeling changes was conducted by Dr. Pamela Horn as appended to the review by Dr. Bob Rappaport, dated February 10, 2013. Dr. Horn reviewed the following material:

IND 29038

- Abuse liability and pharmacokinetic studies
  - CSS reviews of studies OTR-1016, 1018, 1019, 1021, and 1022, DARRTS, 9/21/12
  - Statistical review of study OTR-1018, DARRTS, 8/20/12
  - Clinical Pharmacology review of studies OTR-1016, 1018, and 1021, DARRTS, 9/20/12
  - Study reports OTR-1016, 1018, 1019, 1021, and 1022, submitted to IND 9/17/10
  - Pharmacy instruction manuals OTR-1018 and 1021

NDA 22272:

- In vitro studies: CSS review of the following documents, DARRTS, 9/4/09
  - Comprehensive In Vitro Testing of the Controlled-Release Properties of New OCR Tablets After Physical and Chemical Manipulation – Summary Report

Reference ID: 3294221

- Comprehensive in Vitro Testing of the Controlled-Release Properties of New OCR Tablets After Physical and Chemical Manipulation – Complete Dataset Appendix
- Evaluation of the Resistance to Physical and Chemical Manipulation of Oxycodone HCl (10, 15, 20, 30, 40, 60 and 80 mg) TR Tablets Compared to Currently Marketed OxyContin (10, 15, 20, 30, 40, 60 and 80 mg)
- Protocol for Creating Particle Size Fractions by Crushing and Milling Extended Release Oxycodone HCl Tablets - OxTR In Vitro Testing Plan - Experiments 2a, b and 5a, b, c
- Protocol TTP-PMP-M0043.00 - "Simple Extraction: pH-Dependent API Release Study for Extended Release Oxycodone HCl Tablets"
- Protocol for Smoking (Inhalation) Testing of Physically Manipulated Extended Release Tablets Containing Oxycodone HCl
- Validation Protocol for Simple Extraction Testing of Physically Manipulated Extended Release Tablets Containing Oxycodone HCl

The applicant proposed the changes to Section 9 Drug Abuse and Dependence as shown in the following table. The labeling language is in the left column and the support for the language is in the right column.

(b) (4)

[redacted]

Reference ID: 3294221

(b) (4)

[redacted]

Reference ID: 3294221

(b) (4)	

In deciding what data to include in the labeling, consideration was given to the intended target audience. In this case, in addition to the prescriber, there will be many stakeholders interested in understanding the potential effects of the abuse-deterrent changes to the formulation of OxyContin on the different routes of abuse. Therefore, the study results have been provided in table format with median and mean values, as a figure representing the continuous responder function for drug liking, and as text describing key cutoff points (e.g. no reduction, some reduction, 30% reduction, and 50% reduction in drug liking) in the responder analysis.

The following table represents the final agreed-upon language for the package insert.

Reference ID: 3294221

Risks Specific to Abuse of OxyContin OxyContin is for oral use only. Abuse of OxyContin poses a risk of overdose and death. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk of overdose or death is increased with concurrent use of OxyContin with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OxyContin enhances drug release and increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in OxyContin can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.	This first paragraph is not truly specific to OxyContin but is important to underscore in the context of discussing possible abuse. The inactive ingredients in this formulation, if injected, would risk the types of injury listed. The risk of endocarditis, valvular injury and infection is general
Abuse Deterrence Studies	This is a new title for this section, added to direct the reader to the specific studies of abuse-deterrent characteristics.
OxyContin is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OxyContin resulting from a change in formulation, in this section, the original formulation of OxyContin, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as OxyContin.	The first sentence represents a general statement that is included because later data support the relevance.
In Vitro Testing In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of	This is a restatement of the proposed first paragraph from the sponsor based on the following material: March 30, 2009 Complete Response: Comprehensive *in vitro* Testing –

Reference ID: 3294221

these studies also support this finding for OxyContin relative to an immediate-release oxycodone. When subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.	Summary Report: [3.2.P.2 Pharmaceutical Development, Sequence 0020] Experiment 1: Mechanical Fractionation of Tablets Experiment 2: Extraction in Water Experiment 3: Dissolution in Ethanol Experiment 4: Extraction in Advanced Solvents Experiment 5: Syringability, Injectability and Vaporization for Inhalation
(b) (4)	
Clinical Study In a randomized, double-blind, placebo-controlled, 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OxyContin 30 mg tablets, coarsely crushed OxyContin 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OxyContin, finely crushed original OxyContin, and powdered oxycodone HCl are described below. Drug-liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response (‘definitely would not take drug again’)	This section comes from the following study: September 16, 2010 Information Amendment [Sequence 0025, Serial Number 0559 to oxycodone IND 029038]: OTR 1018 entitled : “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”.

Reference ID: 3294221

and 100 represents the strongest positive response ('definitely would to take drug again').

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in (b) (4) (n=10) of subjects with finely crushed OxyContin, compared with (b) (4) (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OxyContin was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 2.

Table 2. Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

VAS Scale (100 mm)*		OxyContin (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

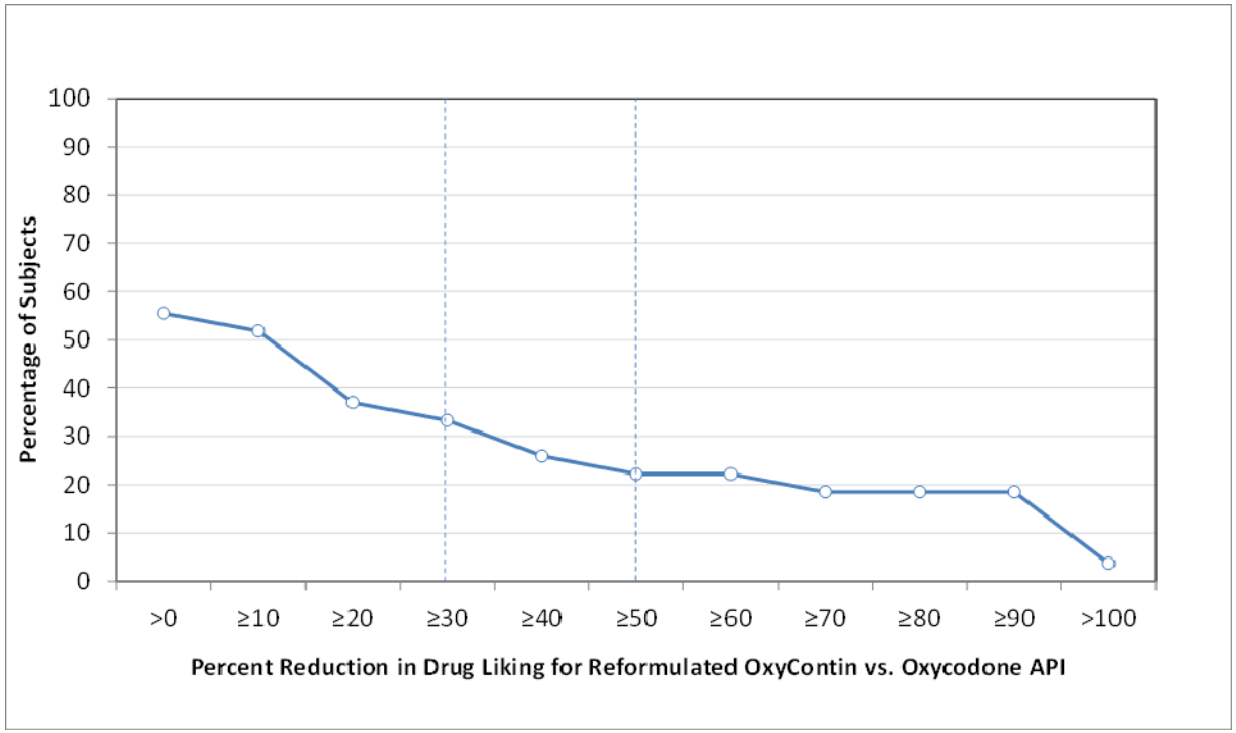
* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OxyContin compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OxyContin vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OxyContin relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OxyContin relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with

DAAAP and CSS reviewed the study protocol and results and concluded that the study was properly designed and conducted. The data describe responses that support the conclusions described below.

The figure, a continuous responder function, represents an additional analysis by FDA. This figure permits the reader to see that relative to plain oxycodone powder, what percent of subjects experienced a reduction in drug liking over the full range from no reduction to total reduction. Any

Reference ID: 3294221

OxyContin compared to oxycodone HCl, and approximately 22% (n= 6) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to oxycodone HCl. **Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OxyContin vs. oxycodone HCl, N=27 Following Intranasal Administration**  	future product can conduct the same study with a comparison to powdered oxycodone and provide the same analysis.
(Note to sponsor: change the title of x-axis to read "Percent Reduction in Drug Liking for Finely Crushed OxyContin vs. Powdered Oxycodone HCl Following Intranasal Administration") The results of a similar analysis of drug liking for finely crushed OxyContin relative to finely crushed original OxyContin, were comparable to the results of finely crushed OxyContin relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no	The sponsor felt that the reader would want to know how the new and old formulations of OxyContin would compare for drug liking. Rather than include another figure, a description of the results was included. The continuous responder

Reference ID: 3294221

reduction in liking with OxyContin relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n= 8) of subjects had a reduction of at least 50% in drug liking with OxyContin compared to original OxyContin.	function is not a common analysis and the natural tendency for the reader is to compare to figures, when, in this case, that is not the correct approach to understand these analyses.
Summary The in vitro data demonstrate that OxyContin has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the in vitro data, also indicate that OxyContin has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OxyContin by these routes as well as the oral route is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OxyContin on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.	These summary statements are derived from suggested language in the draft Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling. The in vitro data are sufficient to show that the new formulation makes injection difficult. Taken together, the clinical liking data and the in vitro data support that the new formulation is likely to result in a meaningful reduction in intranasal abuse. (b) (4)

Reference ID: 3294221

	(b) (4)
OxyContin contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal and illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OxyContin can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.	Restatement of basic risk information to provide context for the study findings.

Reference ID: 3294221

Summary

The addition of in vitro and in vivo study results describing the abuse-deterrent characteristics of the new formulation of OxyContin represents an important advance in labeling products intended to reduce the abuse of opioid analgesics. The development of formulations intended to deter abuse is one step toward creating safer opioid analgesics. As noted in the draft Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling:

> The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. Therefore, FDA will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.

The data and interpretation of the data from the in vitro and in vivo studies added to the OxyContin package insert describe the properties of the new formulation while acknowledging that, as opioid analgesics must be able to deliver the opioid to patients for the management of pain, the extent to which an abuse-deterrent product is able to reduce abuse will never be absolute. Also, abuse-deterrence properties must always be evaluated relative to a comparator that can provide context to the findings.

This action is consistent with the labeling standards set forth in the memo by Dr. Douglas Throckmorton dated April 15, 2013.

Reference ID: 3294221

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

/s/

SHARON H HERTZ
04/16/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Memorandum

To: Douglas Throckmorton, MD

From: Gerald Dal Pan, MD, MHS

Date: April 12, 2013

Re: Office-level Memorandum on Purdue's Reformulated OxyContin

---

To assess the impact of Purdue Pharma's (Purdue) reformulation of OxyContin on OxyContin abuse, several investigations have addressed changes in the prevalence of OxyContin abuse and the routes by which OxyContin is abused. Staff in OSE's Division of Epidemiology II have reviewed reports of Purdue's investigations and two investigations conducted by Research Triangle Institute.[1,2,3,4] This memo focuses on five investigations that both are reasonably well designed and contain sufficient data for review.[5] While some investigations suggest a decline in some aspects of OxyContin abuse, particularly via non-oral routes, these findings are not supported by other data. Most of the investigations report either incomplete data or no data at all. No robust data on overdose or death are available. Taken as a whole, these investigations suggest, but do not confirm, that the reformulation of OxyContin has resulted in a decline in non-oral abuse. Furthermore, the data available at this time cannot support a robust conclusion that the reformulation of OxyContin is responsible for an overall decline in OxyContin abuse.

---

[1] Trinidad, J. & Dormitzer, C. (2012). *Review of "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011)"*. FDA/CDER/OSE. Submitted to DARRTS on Apr 27, 2012, for NDA #022272.

[2] Trinidad, J., Dormitzer, C., & Kornegay, C. (2013). *Review of "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"*. FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.

[3] Trinidad, J. (2013). *Addendum to Review of "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" – Client Treatment Study, National Survey on Drug Use and Health, National Poison Data System, and ARGUS*. FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.

[4] Trinidad, J. (2013). *Discussion on Postmarketing Data for Reformulated OxyContin®.* FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038

[5] The five investigations are NAVIPPRO, the Client Treatment Study, the National Survey of Drug Use and Health (NSDUH), the RADARS System Poison Control Center Program, and the National Poison Data System (NPDS).

Reference ID: 3292602

Changes in Overall Abuse

Using data from standardized self-administered questionnaires completed by clients entering substance abuse treatment centers, the NAVIPPRO investigation examined the prevalence of OxyContin abuse in the 30 days prior to admission. Among persons reporting prescription opioid abuse, the prevalence of reformulated OxyContin abuse after its introduction to the market (12.1%) was 49% lower than the prevalence of original OxyContin abuse before the introduction of the reformulated version (b) (4). Similarly, among all clients, prevalence of OxyContin abuse (regardless of formulation) statistically significantly declined from (b) (4) before, to (b) (4) after, the introduction of the reformulation. This finding, however, does not portray a complete picture of the extent of abuse of extended-release oxycodone, as abuse of original OxyContin persisted seven quarter-years after the introduction of reformulated OxyContin. In addition, some of the decline in the prevalence of abuse of extended-release oxycodone can be attributed to the cessation of the distribution of generic formulations before the introduction of reformulated OxyContin; however, abuse of generic formulations of extended-release oxycodone persisted after the introduction of reformulated OxyContin, though not to the same extent as abuse of original OxyContin. Thus, further study of the prevalence of abuse of reformulated OxyContin compared to the prevalence of abuse of original OxyContin must continue in order to determine the significance of these findings. At this time, the NAVIPPRO findings do not provide a quantitative estimate of the extent of reduction that is attributable to the reformulation.

Similar to the NAVIPPRO investigation, the Client Treatment Study (CTS) investigation, which was independently conducted by Research Triangle Institute on behalf of a commercial sponsor other than Purdue, assessed trends in the prevalence of OxyContin abuse by examining the prevalence of past 30-day abuse among clients entering a random sample of approximately (b) (4) publicly funded substance abuse treatment centers. This investigation found that, on average, 2.6% of clients admitted to substance abuse treatment centers one year prior to the introduction of reformulated OxyContin reported past 30-day abuse of OxyContin, while 2.9% reported past 30-day OxyContin abuse one year afterwards. There is quarter-to-quarter variability in these data, and there was a trend toward increasing OxyContin abuse just prior to the introduction of reformulated OxyContin. While the CTS investigation does not document a decrease in OxyContin abuse, the significance of and reason for the observed increase is not clear. It is also not clear why two different samples of addiction treatment centers (i.e., NAVIPPRO and CTS) report very different findings on the prevalence of reported OxyContin abuse. These differences need to be explored further before conclusions can be drawn as to which estimates best reflect a true population-based estimate.

The National Survey of Drug Use and Health (NSDUH) investigation, which surveys a representative sample of the non-institutionalized general U.S. population, found no significant change in the prevalence of non-medical OxyContin use, measured as the percent of respondents reporting non-medical OxyContin use in the 30 days prior to interview.

Data from the RADARS System Poison Control Center Program and the National Poison Data System were used to assess the extent of OxyContin abuse by measuring the number of poison control calls related to intentional abuse of OxyContin. The RADARS data, which are based on a non-random sample of poison control centers in the U.S., documented that, after the introduction of reformulated OxyContin, there was a 32% relative drop in the number of calls related to OxyContin abuse per unique recipients of OxyContin prescriptions. This decline occurred abruptly after the introduction of reformulated OxyContin, a pattern that is inconsistent with the gradual

Reference ID: 3292602

decline in dispensed prescriptions for OxyContin regardless of formulation. A similar finding was not noted for other prescription opioids. Data from the National Poison Data System, which includes all poison control centers in the United States, found a 30% relative reduction in calls related to OxyContin abuse after the introduction of reformulated OxyContin, and a 19% relative reduction when the calls were adjusted for the number of prescriptions dispensed for OxyContin. This investigation also found a (b) (4) relative reduction in unintentional general exposures to OxyContin, a measure that should not be impacted by the reformulation of OxyContin. Like the NAVIPPRO findings, the findings from poison control center data do not provide a robust quantifiable estimate of the extent of reduction in OxyContin abuse that can be attributed to the reformulation.

Preliminary data from other Purdue-sponsored investigations reported reductions in OxyContin-related drug diversion cases, lower average street prices for reformulated OxyContin compared to original OxyContin, less "doctor-shopping" for reformulated OxyContin, a decline in internet chat room activity on routes of administration and extraction of oxycodone after the reformulation of OxyContin (but no change in abuse-endorsing or abuse-discouraging messages), and lower abuse of reformulated OxyContin among persons who had previously abused original OxyContin in a single county in Kentucky. In an analysis of its spontaneous adverse event reporting database, Purdue reported a decrease in the number of reports of drug abuse, overdose and medication errors with reformulated OxyContin compared to original OxyContin. In an analysis of OxyContin prescribing, Purdue found a modest decrease in the overall number of prescriptions for OxyContin, with more marked reductions in prescriptions to cash-paying patients, prescriptions for the higher strengths (40mg and 80 mg) of OxyContin, and prescriptions written by physicians whose prescribing practices are suggestive of abuse and diversion. While these preliminary findings are consistent with a decrease in drug abuse with reformulated OxyContin compared to original OxyContin, most of these investigations have yet to be validated, and the relationship between the assessed measures and the actual prevalence of drug abuse in the US population is not yet known.

In sum, the above investigations of the overall prevalence of OxyContin abuse used a variety of approaches and outcome measures, yet at this time these investigations cannot support a robust conclusion that the reformulation of OxyContin is responsible for a decline in OxyContin abuse, and cannot provide a valid numerical estimate of a reduction in abuse that could be attributed to the reformulation. Furthermore, the currently available data measure these trends for about 18 months after the introduction of reformulated OxyContin, and thus cannot address whether the observed trends will be sustained.

Changes in Route-specific Abuse

To date, data on changes in route-specific abuse after the introduction of reformulated OxyContin are limited to NAVIPPRO and the Client Treatment Study. The NAVIPPRO investigation, the Purdue-sponsored investigation that best addresses routes of abuse, suggests that non-oral abuse occurred less with reformulated OxyContin than with original OxyContin. In the two years after the introduction of reformulated OxyContin, approximately 40% of persons who abused reformulated OxyContin abused it non-orally, while approximately 70% of persons who abused original OxyContin abused it non-orally during the same time period. The Client Treatment Study investigation found that, among clients who reported OxyContin abuse, the percent of clients usually abusing it non-orally increased from 44% in the year before the introduction of reformulated OxyContin, to 48% in the year afterwards.

Reference ID: 3292602

Because the reformulation of OxyContin was designed to prevent specifically non-oral abuse of OxyContin, it is important to examine the similarities and differences between these two investigations.

First, both investigations use data collected upon intake into substance abuse treatment centers, so that the persons reporting prescription drug abuse will be those who have had sufficient negative consequences of substance abuse that they have sought treatment, or have been forced to receive treatment, in a substance abuse treatment center. Each of the substance abuse treatment centers in the CTS study receives at least some federal funding, while those in the NAVIPPRO investigation receive funding from public, private, or both public and private funding streams. There are not sufficient data to describe more detailed differences between the population in the NAVIPPRO investigation and that in the CTS investigation. The important point is that both investigations focus on populations that are in substance abuse treatment centers, and have had clear problems with substance abuse.

Second, the standardized self-administered questionnaires used in the NAVIPPRO investigation attempted to differentiate between original OxyContin, reformulated OxyContin, and other formulations of extended-release oxycodone. In the CTS investigation, clients in substance abuse treatment centers were asked to identify substances that they used from a list. 'OxyContin' appears on this list, but is not further sub-identified as original OxyContin or reformulated OxyContin. It is also not clear how clients were to report use of generic extended-release oxycodone. Because data from NAVIPPRO show persistence of abuse of original OxyContin for several quarter years after the introduction of reformulated OxyContin, it is important that analyses of route of administration differentiate amongst and assess specific formulations and account for all availabe formulations. In this regard, analyses of route of abuse that differentiate amongst specific formulations are more informative than analyses of route of administration that do not make such a differentiation.

Third, in the NAVIPPRO investigation, the self-administered questionnaire asked clients to report on each route of administration, while in the CTS investigation, clients were asked to list only the 'usual' route of administration.

Fourth, in neither of these studies are data collected on the euphoric effects of using OxyContin via a non-oral route, or the clinical consequences of abusing OxyContin through non-oral routes.

Fifth, the timeframe after introduction of reformulated OxyContin differs between the two studies. Purdue's descriptive statistical analysis of oral and non-oral routes of administration in NAVIPPRO covers the period June 1, 2009 through August 8, 2010 as the "before" period and August 9, 2010 through May 31, 2012 as the "after" period. Before the introduction of reformulated OxyContin, (b) (4) of those who reported abuse of original OxyContin did so via a non-oral route. After the introduction of reformulated OxyContin, (b) (4) of those who reported abuse of original OxyContin did so via a non-oral route, while (b) (4) of those who reported abusing reformulated OxyContin did so via a non-oral route. See Table 1 and Figure 1 below, which is derived from the review of Purdue's study reports, and was generated by the Division of Epidemiology II.

Reference ID: 3292602

Table 1: Percent of adults[†] who, upon stating that they abused extended-release (ER) oxycodone, reported non-oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

[†]Clients admitted into substance abuse treatment more than once are counted multiple times. The data in the tables do not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Figure 1: Percent of adults[α] who reported non-oral routes of administration, among those who abused original or reformulated OxyContin®, from the third quarter of 2009 (3Q2009) to the first quarter of 2012 (1Q2012)

(b) (4)

[†]The figures include data from Jun 1, 2009, which is in 3Q2009, through Sep 30, 2012, which is in 3Q2012.

[‡]Marketing started for reformulated OxyContin® on Aug 9, 2010, which is in 3Q2010.

[α]Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

In the CTS investigation, the primary analysis compared the 12 months prior to the introduction of reformulated OxyContin (3Q2009-2Q2010) to the 12 months after its introduction (3Q2010-2Q2011). The CTS investigation notes a statistically significant increase in the rate of tampering, a

Reference ID: 3292602

measure that is based on reports of non-oral abuse, from 44% to 48% among clients who reported OxyContin abuse. Of note, there was a steady quarter-to-quarter rise in non-oral abuse over the four quarters preceding the introduction of reformulated OxyContin, from a rate of (b) (4) in 3Q2009 to (b) (4) in 2Q2010. At the time of introduction of reformulated OxyContin (3Q2010), the rate of non-oral OxyContin abuse rose to (b) (4), and then fell to a range from (b) (4) over the next three quarters. (See Figure 2). When the analysis was repeated using five or seven quarters of data after the introduction of reformulated OxyContin, the level of non-oral abuse in the Pre-Period (b) (4)) remained lower than that in the Post-Period (b) (4)). Additionally, when the cut-point between the pre- and post-period was changed to 1Q2011, the results were no longer statistically significant.

Figure 2: Percent of Client Treatment Study clients who reported non-oral usual routes of administration if abusing OxyContin®, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Figure 4 of RTI's final study report "Surveillance of OxyContin Abuse: A Time Series Analyses of Nonmedical Use, Abuse, and Tampering Patterns Before and After the Reformulation of OxyContin"

Because the absolute change in non-oral abuse after the introduction of reformulated OxyContin is low (about (b) (4) on an absolute scale) and because the statistical significance of the findings are sensitive to changes in the cut-off points, the findings on non-oral abuse from the CTS investigation are not robust. Additionally, temporal trends in non-oral abuse, as seen in the Pre-Period in the CTS investigation, make simple before-versus-after analyses difficult to interpret. Most importantly, the CTS investigation did not distinguish between formulations of OxyContin in the Post-Period. For that reason, the analysis of non-oral abuse in the NAVIPPRO investigation, which assesses the route of abuse profile for each formulation during the same time period, is preferable to analyses conducted in the CTS investigation. The validity of the method used in NAVIPPRO depends, however, on the accurate classification of original and reformulated OxyContin. Non-differential, or random, misclassification would bias the results toward the null, ie, toward a finding of no difference between the two groups. If this type of misclassification is present, the observed difference in proportion of non-oral abuse between the two formulations would be underestimated. On the other hand, differential, or non-random, misclassification, would

Reference ID: 3292602

bias the results, though one would not know the direction in which they were biased. Indeed, differential misclassification could result in an observed between-formulation difference in proportion of non-oral abuse when such a difference does not actually exist. Because the classification of OxyContin formulation in the NAVIPPRO investigation has not been validated, the extent of misclassification bias, if any, cannot be ascertained. Despite limitations in both analyses, on the whole, the findings on non-oral abuse from the NAVIPPRO investigation appear more reliable than those from the CTS study, and suggest that the proportion of non-oral abuse of reformulated OxyContin is lower than that of original OxyContin.

Changes in Clinical Consequences of OxyContin Abuse

To date, none of the data addressing clinical consequences of OxyContin abuse (such as emergency department visits, overdose, death, or other important clinical measures) is sufficiently developed to warrant review at this time. While one of these Purdue-sponsored investigations plans to assess death, mortality data are not yet available.

Conclusion

Taken as a whole, these investigations suggest, but do not confirm, that the reformulation of OxyContin has resulted in a decline in non-oral abuse. Furthermore, the data available at this time cannot support a robust conclusion that the reformulation of OxyContin is responsible for an overall decline in OxyContin abuse.

****

Reference ID: 3292602

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

/s/

GERALD J DALPAN
04/12/2013

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Addendum to "Review of an Interim Report and Related Abstracts"

Date:	April 12, 2013
Reviewers:	James Phillip Trinidad, M.P.H., M.S., Regulatory Review Officer
	Division of Epidemiology II
Team Leader	Elizabeth Maloney, M.S., Dr.P.H., Epidemiology Team Leader
	Division of Epidemiology II
Division Director	Judy Staffa, Ph.D., R.Ph., Director
	Division of Epidemiology II
Drug Name:	OxyContin®
Subject	Addendum to Review of "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" – Client Treatment Study, National Survey on Drug Use and Health, National Poison Data System, and ARGUS
Application Type/Number:	NDA 22-272; IND 29-038
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2012-2548

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3
1 INTRODUCTION 4
1.1 Background 4
1.2 Regulatory History 4
2 REVIEW METHODS AND MATERIALS 4
3 OVERALL REVIEW RESULTS 5
3.1 Overview of Methods and Findings 7
3.1.1 Client Treatment Study (CTS) Investigation 7
3.1.2 Research Triangle Institutes' National Survey on Drug Use and Health (RTI-NSDUH) Investigation 25
3.1.3 International Drug Safety Database (ARGUS) Investigation Update 33
3.1.4 National Poison Data System (NPDS) Investigation Update 37
4 DISCUSSION 40
5 CONCLUSION 41
6 APPENDIX A: References 43
7 APPENDIX B: Acronyms and their definitions 45
8 APPENDIX C: Drug utilization of extended-release oxycodone, including brand-name OxyContin® 46
9 APPENDIX D: Exposure definitions in NPDS Investigation 47

Reference ID: 3292377

EXECUTIVE SUMMARY

The Division of Epidemiology II reviewed an interim report and related abstracts, submitted by Purdue Pharma L.P. Following review of this interim report, FDA additionally received a report written by Research Triangle Institute (RTI) and updates relating to Purdue's interim report (1; 2). The RTI report contains two investigations, which use the following data sources: the Client Treatment Study (CTS) and the National Survey of Drug Use and Health (RTI-NSDUH). Purdue's update provides additional analyses of data on two investigations: the ARGUS Investigation and the National Poison Data System (NPDS) Investigation.

Notably, among all the investigations reviewed herein and prior, the Research Triangle Institute's (RTI) Client Treatment Study (CTS) Investigation of clients entering substance abuse treatment facilities is the only investigation to find statistically significant increases in the prevalence of OxyContin® abuse after marketing of reformulated OxyContin® (from 2.6% of clients entering substance abuse treatment one year before marketing of reformulated OxyContin® to 2.9% one year afterwards), as well as in the percent of clients usually abusing OxyContin® non-orally (from 44% to 48% of clients who abused OxyContin®). These findings are counter to findings in Purdue's three formal studies of abuse. Meanwhile, RTI's NSDUH Investigation did not find any statistically significant changes in reported non-medical OxyContin® use after marketing of reformulated OxyContin® relative to before marketing of reformulated OxyContin® among a nationally representative sample of the non-institutionalized U.S. general population.

Purdue's ARGUS Investigation update of adverse event reports submitted to Purdue found that, among the 386 case reports of fatal adverse events analyzed and associated with extended-release oxycodone, the number of fatal case reports was much lower two years after marketing started for reformulated OxyContin® than before. However, this decrease may reflect reporting biases inherent in passive surveillance. In addition, approximately 40% of fatal cases identified were not analyzed since they were missing dates of death. The NPDS Investigation update of calls to poison centers found that the average number of OxyContin®-related exposure calls classified as therapeutic errors, general exposures, and adverse reactions was statistically significantly less after marketing of reformulated OxyContin® compared to before marketing. These decreases seemed to reflect the overall decrease in prescriptions dispensed for OxyContin®.

The CTS Investigation and the RTI-NSDUH Investigation do not have sufficient data at this time to be considered formal studies of abuse. Both of these investigations may eventually be considered formal studies of abuse if additional data are collected; it is not clear to the Division of Epidemiology II whether additional data collection is planned. Ideally, the Division of Epidemiology II recommends 3 to 5 years of follow-up for a formal study of reformulated OxyContin® abuse, particularly since investigations in Purdue's postmarketing study program have shown that abuse of original OxyContin®, and possibly other ER oxycodone products, was still prevalent after marketing started for reformulated Oxycontin®.

The CTS Investigation's finding of increases in non-oral OxyContin® abuse materially changes one conclusion in the interim report review, to which this review is an addendum. The interim report review concluded that "any decrease in OxyContin® abuse following the introduction of reformulated OxyContin® was mainly limited to non-oral routes of administration." This conclusion now requires further qualification that increases in non-oral OxyContin® abuse have been observed in one investigation of clients admitted to substance abuse treatment, but not in another investigation assessing a similar population. More years of post-reformulation data on routes of abuse – ideally from both the NAVIPPRO™ Investigation and the CTS Investigation – are needed to assess whether changes in non-oral OxyContin® abuse are genuine and sustained.

Reference ID: 3292377

1 INTRODUCTION

1.1 BACKGROUND

The Division of Epidemiology II previously reviewed an interim report and related abstracts submitted by Purdue Pharma L.P. (3) in response to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products. All documents described investigations assessing the effect that the reformulation of OxyContin® has on OxyContin® abuse and misuse and related outcomes.

Following the Division of Epidemiology II's review of Purdue's interim report and abstracts, the FDA additionally received a report written by Research Triangle Institute (RTI) on OxyContin® abuse before and after marketing of reformulated OxyContin®, in addition to updates to Purdue's interim report (1; 2). The current review focuses on RTI's report and Purdue's updates to their interim report, and is an addendum to the review of Purdue's interim report previously conducted by the Division of Epidemiology II (3).

Appendix B lists all the acronyms used in this review.

1.2 REGULATORY HISTORY

For a more complete description of the regulatory history for reformulated OxyContin®, please refer to the previous interim report review conducted by the Division of Epidemiology II (3).

Reformulated OxyContin® is a single-entity (SE) extended-release (ER) opioid developed by Purdue Pharma L.P. Reformulated OxyContin® was approved for marketing in the U.S. on April 5, 2010. Reformulated OxyContin® replaced the original OxyContin® formulation, which was approved on December 12, 1995. Specifically, on August 5, 2010, Purdue stopped shipping original OxyContin® tablets to pharmacies, and on August 9, 2010, Purdue started shipping only reformulated OxyContin® tablets to pharmacies. However, pharmacies continued to dispense their remaining stock of original OxyContin® after August 5, 2010. See also Appendix C.

Compared to the original formulation, reformulated OxyContin® is more resistant to tampering, specifically, dissolving in liquids, breaking, crushing, or chewing.

Purdue hypothesized that the reformulation of OxyContin® would reduce abuse via injection and snorting, and possibly via oral routes that involve breaking, crushing, or chewing.

2 REVIEW METHODS AND MATERIALS

The materials reviewed in this consult include a report written by Research Triangle Institute (RTI)* and updates for Purdue's postmarketing study program:

- Novak, S. P. (2013). Comment in docket FDA-2013-D-0045. Research Triangle Institute International.
- Purdue Pharma L.P. (2012). Report on the Findings as of December 2012 in Studies #10 and #11 of the 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) focusing on Fatal Events and Unintentional Exposures. Submitted to FDA on Dec 28, 2012, for NDA #022272: SDN 197 / eCTD 0165.

*The Division of Epidemiology II contacted the author of the RTI report for clarification of the results and methods.

Reference ID: 3292377

Appendix A lists all the references cited in this review.

3 OVERALL REVIEW RESULTS

The report by RTI contains two investigations of OxyContin® abuse before and after marketing of reformulated OxyContin®. These investigations use the following data sources:

- The Client Treatment Study (CTS), an evaluation of clients entering substance abuse treatment facilities
- The National Survey of Drug Use and Health (NSDUH), an evaluation of the general, non-institutionalized U.S. population

To reduce confusion with the NSDUH component of the National Surveys Investigation that Purdue is conducting, this review shall refer to RTI's NSDUH component as RTI-NSDUH.

Purdue submitted updates for two investigations: the ARGUS Investigation of adverse events associated with OxyContin® that were reported to Purdue and the National Poison Data System (NPDS) Investigation of calls to poison centers that involved OxyContin®.

The basic design for the four investigations reviewed herein is a comparison of OxyContin® use, misuse, and abuse before versus after marketing started for reformulated OxyContin®.

As per the draft guidance to industry regarding evaluation and labeling of abuse-deterrent opioids (4), three of the investigations reviewed herein are not formal studies of abuse. In brief, formal studies of abuse are designed to:

- assess changes in outcomes that provide meaningful measures of abuse-deterrence
- produce nationally representative data or data from a large geographic region
- assess overall and route-specific abuse, misuse, or both abuse and misuse
- have sufficient data to assess changes in trend and level of OxyContin® abuse, misuse, or both abuse and misuse

As discussed in Section 3.1.1 and Section 3.1.2, respectively, neither the CTS Investigation nor the RTI-NSDUH Investigation has a sufficient number of data points to assess changes in trend and level of OxyContin® abuse. As discussed in Section 3.1.3, the ARGUS Investigation cannot provide a meaningful measure of abuse-deterrence because the outcome of spontaneously reported OxyContin®-related fatalities may be biased. Lastly, as discussed in Section 3.1.4, the update to the NPDS Investigation assessed OxyContin®-related <u>unintentional</u> exposures reported to poison centers, which are not meaningful measures of abuse deterrence; however, the NPDS Investigation is a formal study of abuse since other measures (that is, <u>intentional abuse</u> exposures and <u>intentional misuse</u> exposures) assessed are more meaningful measures to assess abuse and misuse deterrence. For more information on the NPDS Investigation and its measures of intentional abuse and intentional misuse exposures, please refer to the Division of Epidemiology II's review of Purdue's interim report (3).

The design and findings for the studies reviewed herein are summarized in Table 1.

Reference ID: 3292377

Table 1: Summary of two RTI investigations and two updates to Purdue's postmarketing study program aiming to assess the effect of the reformulation of OxyContin® on OxyContin® abuse and misuse

Investigation	Objective	Population	Study periods, relative to marketing of reformulated OxyContin	Opioid exposures	Routes of abuse	Measure and corresponding statistical analysis	Primary findings
Client Treatment Study	- To identify changes in nonmedical use and abuse of OxyContin® and comparator opioids after marketing started for reformulated OxyContin® relative to before marketing started, overall and between subgroups - To identify changes in tampering with OxyContin® and comparator opioids after marketing started for reformulated OxyContin® relative to before marketing started, overall and between subgroups	Clients entering publicly-funded substance abuse treatment centers	**Before**: 3Q2009-2Q2010 **After**: 3Q2010-2Q2011	- OxyContin® - All opioids, excluding OxyContin® - Demerol™ - Dilaudid - Morphine - Oxycodone, excluding OxyContin®	- Any - Non-oral usual route of administration	**1) Prevalence of reported drug abuse,** and **2) percent reporting non-oral usual routes if abusing an opioid -** repeated measures, generalized linear mixed model	- Average quarter-year prevalence of OxyContin® abuse was statistically significantly lower during the pre-reformulated OxyContin® study period (2.6%) than during the post-reformulated OxyContin® study period (2.9%). - Percent of clients who reported usually abusing OxyContin® via non-oral routes of administration statistically significantly increased from 44% during the pre-reformulated OxyContin® study period to 48% during the post-reformulated OxyContin® study period.
RTI-National Survey on Drug Use and Health	- To identify changes in nonmedical use and abuse of OxyContin® and comparator opioids after marketing started for reformulated OxyContin® relative to before marketing started, overall and between subgroups - To identify changes in tampering with OxyContin® and comparator opioids after marketing started for reformulated OxyContin® relative to before marketing started, overall and between subgroups	General U.S. population ages 12+	**Before**: 3Q2009-2Q2010 **After**: 3Q2010-2Q2011	- OxyContin® - Other prescription opioid pain relievers	- Any - Injection (of any prescription opioid)	**1) Prevalence of reported non-medical use -** repeated measures, generalized linear mixed model	- Prevalence of non-medical OxyContin® use did not statistically significantly change after marketing of reformulated OxyContin®.
ARGUS	- To assess changes in the number of adverse event reports reported to Purdue and associated with OxyContin®, before versus after marketing started for reformulated OxyContin®	U.S.	**Before**: 3Q2009-2Q2010 **After**: 3Q2010-2Q2012	- Extended-release oxycodone	Any	**Fatal adverse event reports -** spline Poisson regression	- Among the 61% of case reports of fatal adverse events associated with extended-release oxycodone, the number of fatal case reports was much lower two years after marketing started for reformulated OxyContin®
NPDS	- To assess changes in exposures – according to calls made to U.S. poison centers – associated with OxyContin® and other opioids before and after marketing started for reformulated OxyContin®	U.S. poison control center cases	**Before**: 3Q2009-2Q2010 **After**: 4Q2010-1Q2012	- OxyContin® - Other single-entity oxycodone products	Any	**Unintentional exposures** – Poisson regression	- Quarter-year average number of OxyContin®-related exposure calls for therapeutic errors, general exposures, and adverse reactions was statistically significantly less after marketing of reformulated OxyContin®.

Reference ID: 3292377

3.1 OVERVIEW OF METHODS AND FINDINGS

3.1.1 Client Treatment Study (CTS) Investigation[a]

Objectives

Research Triangle Institute's (RTI's) Client Treatment Study (CTS) Investigation had six objectives:

1. To identify changes in nonmedical use and abuse of OxyContin® between the pre- and post-reformulated OxyContin® study periods
2. To identify changes in OxyContin tampering among nonmedical users and abusers between the pre- and post-reformulated OxyContin® study periods
3. To identify changes in nonmedical use and abuse of Oxycontin® within selected high-risk subgroups between the pre- and post-reformulated OxyContin® study periods
4. To identify changes in OxyContin® tampering among subgroups engaging in nonmedical use of OxyContin® between the pre- and post-reformulated OxyContin® study periods
5. To identify changes in nonmedical use and abuse of comparator products between the pre- and post-reformulated OxyContin® study periods
6. To identify changes in tampering among comparator products between the pre- and post-reformulated OxyContin® study periods

Data source/Data collection

The Client Treatment Study (CTS) Investigation collects client-level data every year from a simple random sample[a] of approximately 600 federally funded substance abuse treatment centers that, in total, serve approximately (b) (4) clients. Data from these (b) (4) centers, as well as other centers, is collected and stored in the Treatment Episode Data Set (TEDS), an administrative data system providing descriptive information about the national flow of admissions to providers of substance abuse treatment (5). Each center providing data to this investigation does the following:

- provides data to TEDS
- can be funded in part by private monies
- is given an expanded data collection instrument for the purposes of standardizing collection of client-level data
- contributes data on clients aged 10+ years in order to receive federal funds

Upon each client's intake, the centers participating in the CTS use a standardized, web-based data collection instrument. The data collection instrument collects information on clients' past 30-day drug abuse and other health measures related to substance abuse (using modified Addiction Severity Index), treatment and recovery, mental and physical health problems, and demographics.

---

[a] Reflects clarifications received from RTI investigator Scott Novak.

Reference ID: 3292377

Regarding past-30 day drug abuse, staff at participating treatment centers use the data collection instrument to ask clients the following:

> "**Abuse of Opioid Products:** Have you used any of the following drugs [to get high], please tell us the number of days and the usual route of administration, such as: 1. Oral, 2. Nasal, 3. Smoking, 4. Non-IV injection, 5. IV"

The opioids inquired about were:

- Heroin (smak, H, junk, skag)
- Morphine
- Dilaudid or hydromorphone
- Demerol™
- Percocet/oxycodone
- Vicodin/hydrocodone
- Codeine brand
- Tylenol 2, 3, 4
- OxyContin® specific (non-generic)
- Non-prescription methadone
- Darvon

The categories "OxyContin® specific (non-generic)" and "Percocet/oxycodone" are mutually exclusive. For example, if a client reported abusing only generic extended-release oxycodone, then the client would be classified as having abused only "Percocet/oxycodone." Similarly, if a client reported abusing only OxyContin®, then the client would be classified as having abused only "OxyContin® specific (non-generic)."

The CTS survey also uses a pill card to help clients identify the drugs they abused. Reporting bias has been minimal when corroborating self-reported abuse with urine toxicology screens; however, no large-scale validation studies have been performed on self-reported drug abuse using the CTS survey.

The CTS definition of past 30-day drug abuse is consistent with the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee definition of drug abuse[b].

Division of Epidemiology II Reviewer comments on data source/data collection

Based on the sampling methods, the CTS Investigation is likely nationally generalizable to clients of federally funded substance abuse treatment centers, which, in turn, are likely generalizable to all substance abuse treatment centers. This is supported by the following:

---

[b] Abuse – as presented by the FDA at the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee, "the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effects it produces" (6)

Reference ID: 3292377

- According to RTI, only a small proportion of centers receive no federal funding.
- RTI states that TEDS captures (b) (4) of clients entering substance abuse treatment nationwide.

However, although RTI states that the CTS consists of a random sample of federally funded substance abuse treatment centers, it is not clear how the CTS is generalizable to licensed treatment centers that are not publicly-funded. RTI stated that the centers sampled for the CTS were sampled so to reflect the larger population of licensed treatment centers in the U.S., but no information was given to address generalizability to non-federally funded treatment centers.

Lastly, RTI did not provide any information on whether clients whose treatment is not funded through public monies were included in the CTS. For some treatment centers, TEDS does not collect client-level data if clients' treatment was privately funded:

> "State substance abuse agencies are requested to provide [TEDS treatment admission] data on all publicly- and privately-funded clients in treatment programs receiving any public funds. There are some instances, however, in which information is provided only for clients whose treatment is funded through public monies."

Overview of methods/analyses

This investigation is a multi-year cross-sectional study that uses survey data from the Client Treatment Study (CTS).

This investigation measures opioid-specific past 30-day drug abuse among clients entering the CTS. Specifically, past 30-day abuse and usual route of administration of abuse was assessed for OxyContin®, which is captured as "OxyContin® specific (non-generic)" and for the following comparator opioids:

- All opioids, excluding OxyContin®
- Demerol™
- Dilaudid
- Morphine
- Oxycodone, excluding OxyContin®

This investigation does not stratify OxyContin® abuse by formulation or capture generic ER oxycodone. The Reviewer assumed that the opioid that comprised 'all opioids' included all opioids assessed by CTS, even though only Demerol™, Dilaudid, morphine, and oxycodone (excluding OxyContin®) were specific comparators assessed in this investigation.

This investigation also assessed "tampering in the past 30-days prior to intake," defined from clients' reported **usual** route of administration. That is, if a client reported a usual route of administration being 'nasal,' 'smoking,' 'non-IV injection,' or 'IV injection,' then that client was considered to be tampering with the opioid.

As specified *a priori*, this investigation assessed abuse of OxyContin® stratified by:

- age: <18 years old and 18+ years old
- treatment type: outpatient, methadone treatment, and detox
- reported abuse of heroin in the past 30-days prior to intake

Reference ID: 3292377

For the primary analyses, this investigation has two study periods: the pre-reformulation study period from the third quarter of 2009 (3Q2009) to the second quarter of 2010 (2Q2010), and the post-reformulation study period (3Q2010 to 2Q2011). Sensitivity analyses varied the length of these two study periods. All data were divided into quarter-year data points.

This investigation had two basic analyses, both of which used a repeated measures, generalized linear mixed model approach:

1. The first analysis compared the aggregated mean prevalence of OxyContin® abuse in the pre-reformulation study period versus the post-reformulation study period.
2. The second analysis compared the trend in prevalence of OxyContin® abuse in the pre-reformulation study period versus the post-reformulation study period.

Division of Epidemiology II Reviewer comments on methods/analyses

Although the CTS survey collects data on the number of days of opioid-specific abuse in the past 30-days, RTI did not provide data on the number of days of abuse, and none of the study objectives address number of days of opioid-specific abuse.

This investigation's analysis on tampering does not consider the fact that clients can abuse prescription opioids via several routes in the past 30-days. In addition, oral routes of administration that involve tampering (for example, chewing) are not specifically captured. For these reasons, the Reviewer has reinterpreted the measure of 'tampering' as non-oral usual route of administration.

RTI also alluded to monthly data upon clarifying this investigation's study design. No figures or tables presented monthly data – only quarter-year data – so it is unclear how monthly prevalence estimates of OxyContin® abuse were modeled or considered in the study design.

In the Reviewer's opinion, a repeated measures analysis is appropriate because the quarter-year prevalence of OxyContin® abuse is measured repeatedly throughout time. Since the unit of analysis was each client entering substance abuse treatment, the mixed effect component could account for within-subject variability for clients who enter into treatment more than once. In addition, the mixed effect component could have been used to account for clustering of clients who enter the same treatment center.

In the Reviewer's opinion, the CTS Investigation could eventually be considered a formal study of abuse if it is conducted again with additional years of data in the post-reformulation study period. Ideally, the Reviewer recommends 3 to 5 years of data collected in the post-reformulation study period to have sufficient data to assess reformulated OxyContin® abuse, particularly since investigations in Purdue's postmarketing study program have shown that abuse of original OxyContin®, and possibly other ER oxycodone products, were still prevalent after marketing started for reformulated Oxycontin®.

RESULTS

Prevalence of abuse of OxyContin® and comparator opioids: Results for objectives 1 and 5

The prevalence of abuse of all opioids was statistically significantly higher during the post-reformulation study period (b) (4)) than during the pre-reformulation study period (b) (4)) (Figure 1 and Table 2). In particular, the mean quarter-year prevalence of OxyContin® abuse was significantly lower during the pre-reformulation study period (2.6% of all substance abuse treatment center clients) than in the post-reformulation study period (2.9%) (Figure 1a and b,

Reference ID: 3292377

Table 2) ($p<0.001$). Sensitivity analyses that considered longer study periods (5 quarter-years before the marketing of reformulated OxyContin® and 7 quarter-years after) did not change this finding.

Figure 1a: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Clarification received from author of RTI report

Reference ID: 3292377

Table 2: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®

(b) (4)

[redacted]

Data source: Clarification received from author of RTI report

RTI stated that the prevalence estimate for OxyContin® abuse of (b) (4) occurring during the post-reformulation study period was a high outlier, and, when excluding this data point, the prevalence of OxyContin® abuse seemed to decline afterwards. In a sensitivity analysis that had the post-reformulation study period start at 1Q2011 (that is, after the occurrence of the outlier) there was no statistically significant difference in mean quarter-year prevalence (b) (4) during the pre-reformulation study period, and (b) (4) afterward, p=0.145).

An analysis comparing trends before and after marketing started for reformulated OxyContin® found that, following a (b) (4) quarter-year increase in prevalence of OxyContin® abuse during the pre-reformulation study period, prevalence of OxyContin® abuse decline by (b) (4) each quarter-year during the post-reformulation study period. This change in trend after marketing started for reformulated OxyContin® was statistically significant (p=0.008).

Compared to the comparator opioids (that is, opioids excluding OxyContin®, oxycodone excluding OxyContin®, morphine, Dilaudid, and Demerol™), OxyContin® was the only opioid to have a statistically significantly higher prevalence of abuse after marketing started for reformulated OxyContin®. That is, while morphine (and possibly the comparator of all opioids excluding Oxycontin®) had a lower prevalence after marketing started for reformulated OxyContin®, prevalence of abuse of the other opioid comparators did not statistically significantly change.

Division of Epidemiology II Reviewer comments on results for objectives 1 and 5

When considering all the investigations reviewed prior (3) and within this current review, the CTS Investigation is the only investigation that found <u>increases</u> in the prevalence of OxyContin® abuse after marketing started for reformulated Oxycontin®. Only in subgroup analyses did this investigation find a lower prevalence of OxyContin® abuse during the post-reformulation study period versus the pre-reformulation study period.

Reference ID: 3292377

Percent of abuse of OxyContin® and comparator opioids via non-oral usual routes of administration: Results for objectives 2 and 6

During the pre-reformulation study period, 44% of clients who reported OxyContin® abuse reported usually abusing it via non-oral routes of administration. During the post-reformulation study period, a statistically significantly higher percentage (48%) of those abusing OxyContin® reported non-oral usual routes of administration ($p<0.01$). Sensitivity analyses that considered longer study periods (5 quarter-years before marketing of reformulated OxyContin® and 7 quarter-years after) did not appreciably change this finding (b) (4) during the pre-reformulation study period, (b) (4) during the post-reformulation study period, statistical significance not stated).

The quarter-year trend in the percent of clients who reported non-oral usual routes of administration if abusing OxyContin® did not statistically significant change between study periods. As Figure 2 suggests, among those who abused OxyContin®, there may have been an increase in the percent of clients reporting non-oral usual routes of administration during the pre-reformulation study period, but the trend did not reach statistical significance.

Figure 2: Percent of Client Treatment Study clients who reported non-oral usual routes of administration if abusing OxyContin®, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Clarification received from author of RTI report

Four comparator opioids (that is, oxycodone excluding OxyContin®, morphine, Dilaudid, and Demerol™) also had a statistically significantly higher percent of clients reporting non-oral usual routes of administration if abusing the respective opioids (Figure 3). For the four comparator opioids, the trend in the percent reporting non-oral usual routes of administration during the pre-reformulation study period was increasing, but was steady during the post-reformulation study period (statistically significant difference using a pre-post trend test).

Reference ID: 3292377

Figure 3: Percent of clients who, upon stating that they abused specific opioids, reported usually abusing the opioids via non-oral routes of administration, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Clarification received from author of RTI report

Division of Epidemiology II Reviewer comments on results for objectives 2 and 6

No analysis in this investigation found that the percentage of clients who abused OxyContin® usually via non-oral routes of administration was lower during the post-reformulation study period relative to during the pre-reformulation study period.

The Reviewer noted that, among those who abused OxyContin®, the percentage of clients who usually abused it non-orally was much higher in 3Q2010 – when reformulated OxyContin® was introduced to the market – than during all four quarters of the pre-reformulation study period. This potential high outlier in 3Q2010 was in the post-reformulation study period, and any effect of the reformulation of OxyContin® on OxyContin® abuse may not be observed until after this quarter-year. Still, a sensitivity analysis, which had the post-reformulation study period start at 1Q2011, after this high percentage estimate, found no statistically significant difference in the percent of clients reporting non-oral usual routes of administration if abusing OxyContin® (b) (4) during the pre-reformulation study period, and (b) (4) afterward, p=0.270). So, a decrease in non-oral usual routes of administration was not found even in this sensitivity analysis.

Prevalence of OxyContin® abuse among selected subgroups: Results for objective 3

The CTS Investigation assessed OxyContin® abuse by age group, treatment modality, and heroin use. Approximately (b) (4) of clients were 18 years old or older. Approximately (b) (4) of clients in the Client Treatment Study were treated as outpatients. The other (b) (4) of clients in the Client Treatment Study entered detox treatment or methadone treatment.

Pre- to post-reformulation changes in the prevalence of OxyContin® abuse were statistically significantly different by age group ($p<0.001$) and treatment type ($p<0.001$). Although RTI did not report whether changes in the prevalence of Oxycontin® abuse were statistically significantly

Reference ID: 3292377

different by reported heroin use in the past 30-days prior to intake, it was apparent that reported heroin use is associated with changes in the prevalence of OxyContin® abuse (see Table 3 and Figure 4c).

Figure 4a-c and Table 3 summarize how the prevalence of OxyContin® abuse changed between the study periods, stratified by subgroups. Although significance testing was conducted on changes in trends stratified by subgroups, RTI did not provide information for most subgroups on the trends of OxyContin® abuse during each study period. Because the confidence intervals are suppressed in the figures, it cannot be determined from visual inspection of these figures whether prevalence of Oxycontin® abuse increased, decreased, or stayed the same throughout each study period.

Figure 4a: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®, by age group

(b) (4)

Reference ID: 3292377

Figure 4b: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®, by treatment modality

(b) (4)

Figure 4c: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®, by reported heroin use in the past 30-days prior to intake

(b) (4)

Data source: Clarification received from author of RTI report

Reference ID: 3292377

Table 3: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®, by subgroup

(b) (4)

Data source: Clarification received from author of RTI report

†The Reviewer noted that, in contrast to this table's prevalences for outpatient clients, Figure 4b above depicts a lower prevalence in the post-reformulation study period than in the pre-reformulation study period. One possible reason for this discrepancy is that these prevalences may be incorrect.

‡The Reviewer used the estimates presented in Figure 4c to calculate the prevalence of OxyContin® abuse among clients who did not report past-30 day abuse of heroin. Because the estimates contain imprecision (that is, there are confidence intervals for the estimates in Figure 4c), these prevalences are approximate.

Percent of OxyContin® abuse via non-oral usual routes of administration, by subgroup: Results for objective 4

Among clients aged 18+ who abused OxyContin®, the percent who reported non-oral usual routes of administration was statistically significantly higher after marketing of reformulated OxyContin started compared to before; conversely, among clients aged <18 who abused OxyContin®, there was no statistically significant change in the percent who reported non-oral usual routes of administration (Table 4). Among clients who abused OxyContin®, those who abused heroin were significantly more likely to report non-oral usual routes of administration than those who did not abuse heroin. However, when stratified by heroin abuse, the percent of clients who reported non-oral usual routes of administration if abusing OxyContin® did not significantly change after marketing of reformulated OxyContin®.

RTI did not present results on non-oral usual routes of administration by treatment modality.

Reference ID: 3292377

Table 4: Percent of clients who, upon stating that they abused OxyContin®, reported usually abusing OxyContin® via non-oral routes of administration, before and after marketing of reformulated OxyContin®, by subgroup

(b) (4)

[redacted]

Note: The Client Treatment Study did not provide results on non-oral usual routes of administration stratified by treatment type.
Data source: Clarification received from author of RTI report

Division of Epidemiology II Reviewer comments on results for all objectives

For most analyses, the Client Treatment Study (CTS) Investigation did not find statistically significant decreases in the prevalence of OxyContin® abuse among clients entering substance abuse treatment after marketing started for reformulated OxyContin®. In fact, many analyses found statistically significantly increases in the prevalence of OxyContin® abuse.

Similarly, among clients abusing OxyContin®, most analyses found that the percent of clients who reported non-oral usual routes of administration was also higher during the post-reformulation versus the pre-reformulation study period. In addition, no analysis found a statistically significant decrease in non-oral usual routes of administration for OxyContin® abuse.

Only certain subgroups had a statistically significantly lower prevalence of OxyContin® abuse during the post-reformulation study period, including the following:

- ages <18 years old
- those who entered detox
- those who reported heroin abuse in the past 30-days prior to substance abuse treatment intake

The relative importance of analyses of all clients compared to analyses of subgroups cannot be determined at this time, and RTI did not provide insight as to what changes in OxyContin® would be expected among the selected subgroups.

This investigation did not integrate the assessments on level (that is, prevalence of OxyContin® abuse) and trend (that is, prevalence of OxyContin® abuse over time). Therefore, in the Reviewer's opinion, it cannot be determined at this time whether the higher prevalence of OxyContin® abuse in the post-reformulation study period is expected given the increasing trends in prevalence of OxyContin® abuse in the pre-reformulation study period.

Reference ID: 3292377

The CTS Investigation and NAVIPPRO™ Investigation - a formal study of abuse in Purdue's postmarketing study program for reformulated OxyContin® - share some similarities methodologically, but yield divergent results (Table 5). Specifically, although both investigations examine the prevalence of OxyContin® abuse among clients of substance abuse treatment centers, the NAVIPPRO™ Investigation found a lower prevalence of OxyContin® abuse during the post-reformulation study period relative to the pre-reformulation study period, while the CTS Investigation did not.

Reference ID: 3292377

Table 5: Comparison of selected study characteristics between the Client Treatment Study Investigation and the NAVIPPRO™ Investigation

Characteristic	Client Treatment Study	NAVIPPRO™ Study as per the primary analyses for the July 2012 interim report
Funder of study	(b) (4)	Purdue
Data source		Adult clients entering a non-random sample of publicly and privately funded substance abuse treatment centers, all which collected reformulated OxyContin® data during the post-reformulated OxyContin® study period.
Settings of care for data source (7)		Outpatient / non-methadone: (b) (4) Methadone treatment: (b) (4) Inpatient or residential (b) (4) Correctional setting (for example, drug court, probation/parole, and DUI/DWI evaluation): (b) (4) Other: (b) (4)
Study periods		Pre-reformulated OxyContin®: Jul 1, 2009-Aug 8, 2010 Post-reformulated OxyContin®: Aug 9, 2010-Mar 31, 2012
Data collection tool for exposure ascertainment		A self-administered standardized, computer-based data collection tool containing visual and audio aids to help identify drugs of abuse
ER oxycodone formulations assessed	OxyContin®	• All ER oxycodone† • Other ER oxycodone (excluding OxyContin®† • All OxyContin® • Original OxyContin® • Reformulated OxyContin®
Definition of abuse	(b) (4)	Use of an opioid analgesic in the past 30 days by an individual in substance abuse treatment that is not strictly in accordance with physician instructions

Reference ID: 3292377

Measure of abuse	• Prevalence of OxyContin® among clients of substance abuse treatment centers. • Percent of clients reporting non-oral usual routes of administration if abusing OxyContin®	• Prevalence of OxyContin® among clients of substance abuse treatment centers. • Percent of clients reporting a non-oral or oral route of administration if abusing OxyContin® (see below) • Number of days of OxyContin® abuse in the past 30-days
Routes of administration assessed	Any route and non-oral usual routes of administration	Any route, non-oral, oral, snorting, smoking, or injection
Prevalence of ER oxycodone abuse among all clients, pre-reformulated OxyContin® study period	OxyContin®: 2.6%	• All ER oxycodone†: (b) (4) • Other ER oxycodone (excluding OxyContin®† (b • All OxyContin®: (b) (4) • Original OxyContin®: (b) (4) • Reformulated OxyContin®: (b) (4)
Prevalence of ER oxycodone abuse, post-reformulated OxyContin® study period	OxyContin®: 2.9%	• All ER oxycodone†: (b) (4) • Other ER oxycodone (excluding OxyContin®† (b • All OxyContin® (b) (4) • Original OxyContin®: (b) (4) • Reformulated OxyContin®: (b) (4)
Results for non-oral routes of administration, pre-reformulated OxyContin® study period	Percent of clients reporting non-oral **usual** routes of administration if abusing OxyContin®: 44%	Percent of clients reporting non-oral routes of administration if abusing… • All ER oxycodone†: (b) (4) • Other ER oxycodone (excluding OxyContin®†: (b) (4) • All OxyContin®: (b) (4) • Original OxyContin®: (b) (4) • Reformulated OxyContin®: (b) (4)

Reference ID: 3292377

Results for non-oral routes of administration, post-reformulated OxyContin® study period	Percent of clients reporting non-oral **usual** routes of administration if abusing OxyContin®: 48%	Percent of clients reporting non-oral routes of administration if abusing… • All ER oxycodone†: (b) (4) • Other ER oxycodone (excluding OxyContin®†: (b) (4) • All OxyContin®: (b) (4) • Original OxyContin®: (b) (4) • Reformulated OxyContin®: (b) (4)

† ER oxycodone and other ER oxycodone (excluding OxyContin®) were not analyzed in primary analyses, but at the request of FDA.

Reference ID: 3292377

Overall, prevalence of OxyContin® abuse was much lower in the CTS Investigation than in the NAVIPPRO™ Investigation. This may be a reflection of several differences in the study characteristics between the two investigations (Table 5):

- The two investigations may be generalizable to two different populations of clients entering substance abuse treatment centers. For example, the higher percent of NAVIPPRO™ clients admitted to methadone treatment and inpatient settings of care could suggest a more advanced stage of addiction (and more likelihood of abusing prescription opioids) than the clients in the CTS Investigation, who were primarily admitted into outpatient settings of care.
- The data collection instrument is self-administered in the NAVIPPRO™ Investigation, and administered by staff in the CTS Investigation.
- Ascertainment of OxyContin® abuse seems to be aided visually in both investigations; the NAVIPPRO™ Investigation also uses audio cues, whereas it is not known at this time whether the Client Treatment Study uses audio cues to ascertain OxyContin® abuse.
- The NAVIPPRO™ Investigation's definition of abuse is more inclusive of possible misuse than the CTS Investigation's definition of abuse.

Unlike the CTS Investigation, the NAVIPPRO™ Investigation observed decreases in the prevalence of OxyContin® abuse after marketing of reformulated OxyContin®. Again, this may be a reflection of several differences in the study characteristics between the two studies (Table 5):

- The two investigations may be generalizable to two different populations of clients entering substance abuse treatment centers. For example, if admittance into methadone treatment and inpatient settings of care is a marker for more advanced stages of prescription opioid addiction (including abuse via non-oral routes of administration), then clients in the NAVIPPRO™ Investigation could be more likely to be affected by the reformulation of OxyContin® on abuse – particularly via non-oral routes of abuse – than clients in the CTS Investigation.
- The post-reformulation study period was longer in the NAVIPPRO™ Investigation, so the effect of the reformulation on OxyContin® abuse, if any, may not be fully captured.

It is unclear from the NAVIPPRO™ and CTS investigations how prevalent OxyContin® abuse could be in the absence of abuse of original OxyContin® since abuse of original OxyContin®, and possibly other ER oxycodone products, was still prevalent during the post-reformulation study period (refer to Division of Epidemiology II's review of Purdue's interim report) (3).

The percent of clients who reported non-oral routes of administration was also much lower in the CTS Investigation – this is likely because the CTS does not capture all routes of OxyContin® abuse, only the most usual route of administration.

Assessing **usual** routes of administration in the CTS Investigation can help assess the construct of 'desirability of OxyContin® abuse via non-oral routes of administration.' On the one hand, while assessment of usual routes of administration cannot completely describe the route of administration profile for OxyContin® abuse, this assessment can provide insight as to whether abuse of OxyContin® via non-oral routes of administration continues to be desirable to those who abuse OxyContin®. That is, if the reformulation of OxyContin® truly deterred abuse via non-oral routes of administration, the usual route of administration during the post-reformulation

Reference ID: 3292377

study period would more likely be via an oral route of administration compared to during the pre-reformulation study period.

Given the limitations of the CTS Investigation (particularly the short post-reformulation study period relative to the post-reformulation study period in the NAVIPPRO™ Investigation), it cannot be determined at this time whether an increased percent of clients reporting non-oral usual routes of administration during the post-reformulation study period represents an increased desirability of non-oral abuse of OxyContin® or other factors.

The CTS Investigation attempted to assess changes in the level (that is, prevalence) and trend (that is, prevalence over time) in OxyContin® abuse using methods similar to an interrupted time series approach. However, this investigation did not attempt to integrate assessments of level and trend to answer:

- Was the higher prevalence of OxyContin® abuse during the post-reformulation study period much higher than expected given the increasing trend in prevalence of OxyContin® abuse during pre-reformulation study period?
- What would have been the prevalence of OxyContin® abuse had the prevalence of OxyContin® continued to rise in the fashion observed during the pre-reformulation study period?

Integrating assessments of level and trend could prove to be more informative than each assessment by itself, particularly if a longer time frame than one year before and after marketing of reformulated OxyContin® is used.

Reference ID: 3292377

3.1.2 Research Triangle Institutes' National Survey on Drug Use and Health (RTI-NSDUH) Investigation[a]

Objectives

The RTI-NSDUH Investigation had the same six objectives as the CTS Investigation:

1. To identify changes in nonmedical use and abuse of OxyContin® between pre- and post-reformulated OxyContin® study periods
2. To identify changes in OxyContin tampering among nonmedical users and abusers between the pre- and post-reformulated OxyContin® study periods
3. To identify changes in nonmedical use and abuse of Oxycontin® within selected high-risk subgroups between the pre- and post-reformulated OxyContin® study periods
4. To identify changes in OxyContin® tampering among subgroups engaging in nonmedical use of OxyContin® between the pre- and post-reformulated OxyContin® study periods
5. To identify changes in nonmedical use and abuse of comparator products between the pre- and post-reformulated OxyContin® study periods
6. To identify changes in tampering among comparator products between the pre- and post-reformulated OxyContin® study periods

Data source/Data collection

The National Survey on Drug Use and Health (NSDUH), which is maintained by the Substance Abuse and Mental Health Administration (SAMHSA), collects nationally representative annual data on the characteristics of non-medical pharmaceutical opioid use among non-institutionalized children, young adults, and older adults. NSDUH does not distinguish between drug abuse and drug misuse, according to the definitions of abuse[b] and misuse[c] that were used at the October 2010 Advisory Committee. Therefore, although the interim report infers that the results are specific to abuse, the results could reflect both abuse and misuse.

NSDUH uses a standardized computer-assisted self-interviewing technology to capture self-reported non-medical use of opioid pharmaceuticals. NSDUH respondents are asked:

- "Now we have some questions about drugs that people are supposed to take only if they have a prescription from a doctor. We are only interested in your use of a drug if:
    - the drug was not prescribed for you, or
    - you took the drug only for the experience or feeling it caused."

To help NSDUH respondents identify drugs that they abused, respondents use colored pill cards with pictures of different prescription opioids and names of the respective opioids in question.

Specifically, according to the 2007 NSDUH Questionnaire, respondents are asked if they used the following prescription opioids non-medically ever in the respondent's lifetime, in the past year, and in the past month (8):

---

[c] Misuse – as presented by the FDA in the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee, "the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner" (6)

Reference ID: 3292377

- Darvocet, Darvon, or Tylenol with codeine
- Percocet, Percodan, or Tylox
- Vicodin, Lortab, or Lorcet
- Codeine,
- Demerol™
- Dilaudid
- Fioricet
- Fiorinol
- Hydrocodone
- Methadone
- Morphine
- OxyContin
- Phenaphen with Codeine
- Propoxyphene
- SK-65
- Stadol
- Talacen
- Talwin
- Talwin NX
- Tramadol
- Ultram
- Any other prescription pain reliever

NSDUH collects information on injection of OxyContin® anytime during the respondent's lifetime, but does not collect information on any other routes of administration (8). Specifically, NSDUH asks respondents whether they abused any drug via injection, and, if so, which drug(s).

Overview of methods/analyses

This investigation is a serial cross-sectional study that uses survey data from the National Study on Drug Use and Health (NSDUH).

The primary opioid of interest in this investigation was OxyContin®, with no stratification by formulation or consideration of generic or other ER oxycodone formulations (for example, Mexican and Canadian OxyContin®), and the comparator opioid was other prescription opioid pain relievers, excluding OxyContin®.

This investigation assessed past 30-day non-medical use of OxyContin®. In addition, this investigation assessed 'tampering among past 30-day nonmedical users of OxyContin®,' defined as the percent of persons who reported injecting <u>any opioid</u> among those who reported non-medical use of OxyContin®.

Reference ID: 3292377

For the primary analyses, this investigation has two study periods: the pre-reformulation study period from the third quarter of 2009 (3Q2009) to the second quarter of 2010 (2Q2010), and the post-reformulation study period (3Q2010 to 2Q2011). At the time this report was produced, data for only the first two quarter-years of 2011 were available. Sensitivity analyses varied the length of the study periods. All data was divided into quarter-year data points or presented as annual data points.

To estimate quarter-year data, this investigation adjusted the sampling weights according to the quarter-year U.S. population (that is, the analysis weight was multiplied by the number of quarter-years each year was providing data).

As specified *a priori*, this investigation assessed abuse of OxyContin® stratified by:

- age: 12-17 years old and 18+ years old
- reported abuse of heroin in the past 30-days

This investigation had two basic analyses, both which used a repeated measures, generalized linear mixed model approach:

1. The first analysis compared the aggregated mean prevalence of non-medical OxyContin® use in the pre-reformulation study period versus the post-reformulation study period.
2. The second analysis compared the trend in prevalence of non-medical OxyContin® use in the pre-reformulation study period versus the post-reformulation study period.

Division of Epidemiology II Reviewer comments on methods/analyses

NSDUH's data collection instrument does not specifically assess non-medical use of generic and other ER oxycodone. Thus, some respondents who abused generic and other ER oxycodone products may report OxyContin® abuse since it is the closest in formulation to, and recognizable as the brand name of, ER oxycodone. However, other respondents who abused generic and other ER oxycodone products may report these products as "any other prescription pain reliever" or not report these products at all.

The measure of 'tampering' assessed in this investigation is not specific to OxyContin® and is not sensitive to other forms of routes of administration that require tampering, such as snorting and chewing. In addition, misclassification of the time when injecting the opioids occurred is likely to exist since NSDUH only measures non-medical opioid use via injection <u>during the respondent's lifetime,</u> not specifically in the past 30 days<u>.</u>

For these reasons, the Reviewer has re-interpreted the measure of 'tampering among past 30-day nonmedical users of OxyContin®' as 'reported opioid injection anytime during persons' lifetime among past 30-day nonmedical users of OxyContin®.'

A repeated measures analysis is appropriate because the quarter-year prevalence of non-medical OxyContin® use is measured repeatedly throughout time.

In the Reviewer's opinion, both of Purdue's National Surveys Investigation, specifically the NSDUH component, and the RTI-NSDUH Investigation do not have sufficient annual or quarter-year data at this time to be considered formal studies of abuse. However, both investigations may eventually be considered formal studies of abuse if additional data are collected. Ideally, the Reviewer recommends 3 to 5 years of follow-up for a formal study of reformulated OxyContin® abuse, particularly since investigations in Purdue's postmarketing study program have shown that abuse of original OxyContin®, and possibly other ER oxycodone products, was still prevalent after marketing started for reformulated Oxycontin®.

Reference ID: 3292377

Prevalence of abuse of OxyContin® and other opioid pain relievers: Results for objectives 1 and 5

The prevalence of non-medical OxyContin® use was elevated in 2010 and 2011 relative to prior years when only original OxyContin® was marketed (Figure 5). Indeed, from 3Q2009 to 2Q2010 the prevalence was (b) (4) among persons aged 12+ years, and from 3Q2010 and 2Q2011 the prevalence was (b) (4) among persons in the same age range. This comparison was not statistically different.

Figure 5: Annual prevalence of past 30-day non-medical OxyContin® use among NSDUH respondents, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Clarification received from author of RTI report

RTI stated that the estimated number of persons using OxyContin® non-medically may have increased by (b) (4) in the post-reformulation study period compared to the pre-reformulation study period. However, RTI also stated that the standard error for the estimates were large (not shown).

The prevalence of non-medical use of other prescription opioid pain relievers did not statistically significantly change (Figure 6). Specifically, the prevalence of non-medical use of these products was (b) (4) during the pre-reformulation study period, and (b) (4) during the post-reformulation study period.

Reference ID: 3292377

Figure 6: Quarter-year prevalence of past 30-day non-medical use of OxyContin® or other prescription opioids among NSDUH respondents, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Clarification received from author of RTI report

The trend (that is, quarter-year rate of change) in the prevalence of non-medical OxyContin® use was not statistically different between the pre-reformulation study period (3Q2009-2Q2010) and the post-reformulation study period (3Q2010-2Q2011).

Meanwhile, the trend statistically significantly changed for other prescription opioid pain relievers. Specifically, prevalence of non-medical use of these products increased, on average, by (b) (4) per quarter during the pre-reformulation study period, but stayed steady during the post-reformulation study period.

Division of Epidemiology II Reviewer comments on results for objectives 1 and 5

No analysis (that is, primary or sensitivity analyses) found a lower prevalence of non-medical OxyContin® use during the post-reformulation study period versus the pre-reformulation study period. This general finding may not be unexpected since that the study population is the general U.S. population, and the reformulation of OxyContin® was designed to affect abuse via non-oral means, which are routes more common among experienced abusers. Thus, changes in the prevalence of non-oral, non-medical OxyContin® use among persons with more prescription opioid abuse experience may be masked by the larger general population with less or no opioid abuse experience.

Prevalence of OxyContin® abuse among selected subgroups: Results for objective 3

Figure 7 shows the quarter-year prevalence of past 30-day non-medical use of OxyContin®, before and after marketing of reformulated OxyContin®, by age group. There were no statistically significant differences in the prevalence of non-medical OxyContin® use before vs.

Reference ID: 3292377

after marketing of reformulated OxyContin® for persons aged 12-17 or for persons aged 18+, and age had no statistically significant effect on prevalence of non-medical OxyContin® use (Figure 7).

Figure 7: Quarter-year prevalence of past 30-day non-medical use of OxyContin® among NSDUH respondents, before and after marketing of reformulated OxyContin®, by age group

(b) (4)

Data source: Clarification received from author of RTI report

This investigation did not conduct a statistical analysis comparing trends in the prevalence of non-medical OxyContin® use in the past 30-days between age groups. However, this investigation did conduct a statistical analysis comparing trends in non-medical use of OxyContin® in the past year between age groups. Results of that analysis revealed that persons aged 12-17 had a (b) (4) increase in the rate of nonmedical use of OxyContin® per quarter compared to adults, although this trend was not statistically significant.

Heroin users were more likely to report non-medical OxyContin® use (Figure 8). Among respondents who did report heroin use, there were statistically significant increases in the prevalence of non-medical OxyContin® use from the pre- to post-reformulation study periods (that is, prevalence increased from (b) (4) of respondents using heroin during the pre-reformulation study period to (b) (4) of respondents during the post-reformulation study period). Over time, non-medical OxyContin® use increased among heroin users.

On the other hand, among respondents who did not report abusing heroin in the past 30-days, there was no statistically significant change in the prevalence, or trend in the prevalence, of non-medical OxyContin® use from the pre- to post-reformulation study period.

Reference ID: 3292377

Figure 8: Prevalence of past 30-day non-medical use of OxyContin®, before and after marketing of reformulated OxyContin®, by reported heroin use.

(b) (4)

Data source: Clarification received from author of RTI report

Results for objectives 2, 4, and 6: Percent of respondents reporting abuse of prescription opioids via injection during their lifetime among respondents who did and did not report abuse of OxyContin®

The percent of respondents who reported injection of prescription opioids during their lifetime among respondents who abused OxyContin® did not statistically significantly change from 3Q2009-2Q2010 (b) (4) to 3Q2010-2Q2011 (b) (4) (Figure 9). RTI concluded that the trends for injection of prescription opioids were similar among those who abused OxyContin® versus other prescription opioids.

Reference ID: 3292377

Figure 9: Percent of respondents reporting lifetime abuse of prescription opioids via injection among respondents who abused other prescription opioids or OxyContin®

(b) (4)

Data source: Clarification received from author of RTI report

Compared to youths aged 12-17, adults were more likely to report injection of prescription opioids in their lifetime if abusing OxyContin®. No other comparisons were performed.

Division of Epidemiology II Reviewer comments on all objectives

For most analyses, the RTI-NSDUH Investigation did not find statistically significant changes in the prevalence of non-medical OxyContin® use after marketing started for reformulated OxyContin® relative to before marketing started. The one exception was for the subgroup of respondents reporting past 30-day heroin use. Among this subgroup, prevalence of non-medical OxyContin® use increased after marketing started for reformulated OxyContin®.

As stated above, the relative importance of analyses of all respondents compared to analyses of subgroups cannot be determined at this time, and RTI did not provide insight as to what changes in non-medical use of OxyContin® would be expected among the selected subgroups.

Reference ID: 3292377

3.1.3 International Drug Safety Database (ARGUS) Investigation Update

Objective

The International Drug Safety Database (ARGUS) Investigation aims to assess changes in the number of adverse event reports associated with the original OxyContin® formulation or reformulated OxyContin® before and after marketing started for reformulated OxyContin®.

Data Source/Data Collection

Data include adverse event reports reported to Purdue as being at least one of four coded case types (drug abuse, intentional drug misuse, overdose, and medication errors).

Overview of methods/analyses

The ARGUS Investigation is a prospective case-series analysis.

The current review considers an updated analysis which assessed case reports of fatality associated with OxyContin® use, abuse, and misuse. The inclusion criteria for case reports were the following:

- Fatal cases originating in the U.S. involving ER oxycodone

Cases having the following characteristics were excluded:

- Cases lacking one or more core elements (that is, a patient, a reporter, a suspect product, or an adverse event)
- Cases with fatalities having a date of death before 3Q2009
- Legal cases originating from report sources related to U.S. litigation

Duplicate cases, identified using age, sex, and event date, were excluded.

Individual case narratives were extracted for reports of fatalities, and evaluated for classification as an overdose-related event or an event related to drug abuse behavior, or both.

All overdose-related events met at least one of the following criteria:

- Overdose or medically related term (for example, drug poisoning, polydrug toxicity, drug intoxication, or overmedicated) was stated verbatim by reporter
- Circumstances surrounding death provided supportive evidence of an overdose-related event (for example, ingestion of many pills, dosing mistake, tampering / snorting / injection of drug, drug obtained and ingested at a party, or ingestion of multiple drugs concomitantly)
- Coroner or physician deemed fatality was associated with opioid overdose or polydrug overdose (with or without toxicology evidence of ingestion)

All events related to drug abuse behavior met at least one of the following criteria:

- Subject currently or previously manipulated ER oxycodone with intention of abuse (for example, crushed and snorted, or dissolved and injected)

Reference ID: 3292377

- ER oxycodone was not prescribed to the subject and/or subject was obtaining drug via multiple healthcare providers, multiple pharmacies, or unlawful transfer(s) (for example, stolen, or received at a party, from parents supply, from the street, or from a pill mill), or any combination of these sources
- Reporter states that subject had or has a history of addiction disorder or drug rehabilitation (or both), or indicated that subject is currently addicted
- Reporter stated that subject had been using illicit drugs (such as heroin, cocaine, or marijuana) alone or in combination with ER oxycodone

The ARGUS Investigation focused on case reports with a date of death (both month and year). Note: For most fatal case reports, the date of receipt of the case report occurs after the actual date of death, that is, there is a lag from death to receipt.

Analyses included:

- Trending the total and overdose-specific cases of fatality per quarter-year
- Averaging the number of fatalities per quarter for three separate study periods.

The three study periods were:

- One year before marketing started for reformulated OxyContin®: 3Q2009-2Q2010
- The first year after marketing started: 3Q2010-2Q2011
- The second year after marketing started: 3Q2011-2Q2012

To evaluate change in the rate of fatalities per quarter-year among the three study periods, a spline Poisson regression was used with a knot at the date when marketing started for reformulated OxyContin®.

Furthermore, sensitivity analyses analyzed fatalities among subgroups to assess how well fatal cases were associated with unintentional overdoses (rather than intentional suicides). These subgroups were: 1) cases excluding those with a textual reference to suicide or homicide, and 2) cases excluding suicide or homicide submitted by a healthcare professional.

Lastly, a sensitivity analysis adjusted for a lag period between event and report date by analyzing overdose reports received anytime up to 2Q2012, received within 6 months of the date of death, and received within 3 months of the date of death.

Preliminary results

Of the 635 cases that met the case inclusion/exclusion criteria, only 386 (61%) had a date of death.

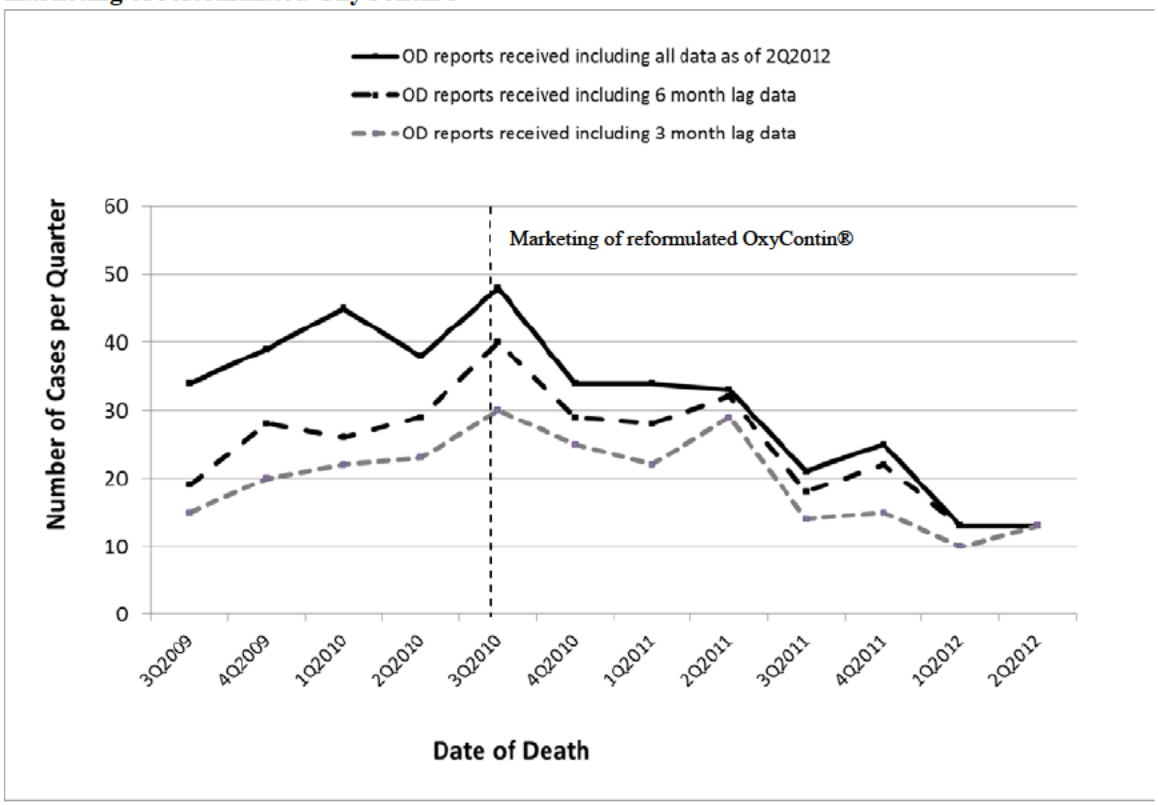
Among the 386 cases, the age distribution and case characteristics (report source, reporter type, use of concomitant medications, and report of autopsy and toxicology test results) were similar among the three study periods.

The number of fatal case reports regarding ER oxycodone was much lower two years after marketing started for reformulated OxyContin® (Figure 10). There were 157 cases with a date of death during 3Q2009-2Q2010, 154 during 3Q2010-2Q2011, and 75 during 3Q2011-2Q2012. Stratification by case type (overdose or overdose with mention of abuse) or exclusion of suicide and homicide cases did not appreciably change this general trend.

Reference ID: 3292377

In an assessment between the effect of lag between date of death and receipt of cases, the number of fatal case reports was, as expected, much lower if only considering cases whose date of receipt was within three months of the date of death. In the Reviewer's opinion, the assessment of lag shows that the number of fatal case reports two years after marketing started for reformulated OxyContin® (3Q2011-2Q2012, approximately 10 to 15 cases) was lower than one year after marketing started (3Q2010-2Q2011, approximately 20 to 30 cases), but only somewhat appreciably lower than one year before marketing started (3Q2009-2Q2010, approximately 15 to 25 cases).

Figure 10: Sensitivity analysis assessing the number of fatal overdose cases per quarter received by the International Drug Safety Database (ARGUS), using a 3-month lag, 6-month lag, or no lag between date of death and receipt date, before (3Q2009-2Q2010) and after (3Q2010-2Q2012) marketing of reformulated OxyContin®



Data Source: Figure 5 of "Report on the Findings as of December 2012 in Studies #10 and #11 of the 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) focusing on Fatal Events and Unintentional Exposures)

In a sensitivity analysis, the ARGUS Investigation found that including the roughly 40% of fatal cases without a date of death did not substantially change the time trends observed with only cases that had dates of death. However, Purdue did not state how they classified the date of death for the cases with missing dates of death. Additionally, no sensitivity analysis of lag could be performed for these cases since the date of death is unknown.

Reference ID: 3292377

Division of Epidemiology II Reviewer comments

Purdue states that the postmarketing data suggest that the reformulation may be having the desired effect of reducing misuse and abuse of OxyContin®. However, since these data represent passive surveillance, these changes may be the result of other factors that affect reporting or interpretation of case reports, such as underreporting, missing information (particularly, missing dates of death), inability to assign causality, recall bias, and confounding (for example, lower milligram strengths of reformulated OxyContin® were dispensed relative to strengths of original OxyContin® during the pre-reformulation study period, as was observed in Purdue's IMS Xponent Investigation (3), so the lower strengths of reformulated OxyContin® dispensed could have contributed to fewer fatal cases) (9). Therefore, in the Reviewer's opinion, the ARGUS Investigation cannot be considered a formal study of abuse because this investigation's measures of abuse-deterrence – that is, spontaneous adverse events related to fatalities, drug abuse, intentional drug misuse, overdose, or medication errors – may be biased by factors that affect passive surveillance.

Reference ID: 3292377

3.1.4 National Poison Data System (NPDS) Investigation Update

Objective

The NPDS Investigation aims to assess changes in exposures – according to calls made to U.S. poison centers – associated with OxyContin® and other opioids before and after marketing started for reformulated OxyContin®.

Data Source/Data Collection

The NPDS Investigation uses data on exposure calls made to all (b) (4)[d] U.S. regional poison control centers. For each exposure case, Specialists in Poison Information ask callers detailed questions to identify the exposure as accurately as possible, including ascertaining an exposure from a drug product's label, shape, color, and imprint. The Specialists in Poison Information also use a nationally standardized data collection tool to code reasons for exposure reported by callers to poison centers (10). Examples of reasons of exposure include "intentional abuse exposure" and "unintentional general exposure" (see Appendix D for full list of reasons of exposure).

Overview of Methods/Analyses

The current review considers an updated analysis of the number of OxyContin®-related unintentional exposure calls related to:

- Therapeutic errors
- General exposures
- Adverse reactions

See Appendix D for definitions of types of exposure calls, including therapeutic errors and general exposures. Purdue has not provided a definition for adverse reactions.

The two study periods were 3Q2009-2Q2010 (that is, before marketing started for reformulated OxyContin®) and 4Q2010-1Q2012 (that is, after marketing started).

The updated analysis compared unintentional exposure calls and the prescription-adjusted[e] rate of unintentional exposure calls for OxyContin® and other SE oxycodone products before and after marketing started for reformulated OxyContin®.

Poisson regression was used to estimate the average quarter-year number of the unintentional exposure calls per study period, the prescription-adjusted average quarter-year number of unintentional exposure calls per study period, and the pre-post change in the number and prescription-adjusted average quarter-year number of unintentional exposure calls and prescriptions dispensed. In addition, the updated analysis included the calculated percent change (from baseline (the 3Q2009-2Q2010) to each subsequent quarter-year) in the number and prescription-adjusted rate of unintentional exposure calls.

---

[d] (b) (4)

[e] IMS Health, Inc., SDI VONA provided data on the number of prescriptions dispensed per product.

Reference ID: 3292377

Preliminary Results

The quarter-year average number of OxyContin®-related exposure calls for therapeutic errors, general exposures, and adverse reactions was statistically significantly less after marketing started for reformulated OxyContin® than before (Table 6 and Figure 11). The relative percent decrease in the quarter-year average number of calls was (b) (4) for unintentional general exposure calls, (b) (4) for unintentional therapeutic error exposure calls, and (b) (4) for adverse reactions.

While the quarter-year average number of general exposure calls for other SE oxycodone products did not statistically significantly change after marketing started for reformulated OxyContin®, there were statistically significant increases in the average number of calls regarding therapeutic errors and adverse reactions related to other SE oxycodone.

Table 6: Unintentional exposure calls for OxyContin® and other single-entity oxycodone products, before (3Q2009-2Q2010) and after (4Q2010-1Q2012) marketing of reformulated OxyContin®

(b) (4)

Data Source: Table 6 of "Report on the Findings as of December 2012 in Studies #10 and #11 of the 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) focusing on Fatal Events and Unintentional Exposures)

Reference ID: 3292377

Figure 11: Percent change from 3Q2009 in the number of unintentional therapeutic error calls (left) and unintentional general exposure calls (right) to the National Poison Data System, regarding OxyContin® and other single-entity (SE) oxycodone products

(b) (4)

(b) (4)

ORF = reformulated OxyContin®

Data Source: Figures 6a and 6b of "Report on the Findings as of December 2012 in Studies #10 and #11 of the 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) focusing on Fatal Events and Unintentional Exposures)

Because the quarter-year number of OxyContin® prescriptions dispensed steadily decreased after marketing started for reformulated OxyContin® (see Figure 13 in Appendix C), the quarter-year rate of OxyContin®-related unintentional therapeutic error calls did not statistically significantly decrease when adjusted for prescriptions dispensed (Figure 12).

Figure 12: Percent change from 3Q2009 in the number of prescriptions dispensed and unintentional therapeutic error calls regarding OxyContin®

(b) (4)

ORF = reformulated OxyContin®

Reference ID: 3292377

The updated analysis also found that the quarter-year average number and quarter-year average prescription-adjusted rate of unintentional general, unintentional therapeutic errors, and adverse reaction exposure calls decreased after marketing started for reformulated OxyContin®, regardless of milligram dosage strength (10 to 30 mg, 40 to 60 mg, or 80 mg).
Purdue concluded that the NPDS data indicate reductions in therapeutic errors, accidental exposures, and adverse reactions.

Division of Epidemiology II Reviewer comments

The effect of the reformulation of OxyContin® on the number of unintentional exposure calls is confounded by the number of prescriptions dispensed for OxyContin® following the introduction of OxyContin® to the market. Indeed, the prescription-adjusted rate of therapeutic error exposure calls did not change after marketing started for reformulated OxyContin®. No analysis assessed the prescription-adjusted rate of adverse events and general exposures.

In the Reviewer's opinion, unintentional general exposures seem to be a less relevant measure than intentional abuse exposures, intentional misuse exposures, and unintentional therapeutic errors for understanding the effect that the reformulation of OxyContin® may have on OxyContin® -related adverse consequences. Indeed, the update did not describe the mechanistic or biological pathway linking the reformulation of OxyContin® to observed reductions in the three unintentional exposure call types assessed. Still, given that unintentional therapeutic errors include unintentional deviations in routes of administration, it may be useful to examine this potential proxy for drug misuse.

4 DISCUSSION

Of all the investigations reviewed herein and prior (3), the Client Treatment Study (CTS) Investigation is the only investigation to find statistically significant increases in the prevalence of OxyContin® abuse, and in the percent of persons abusing OxyContin® non-orally, after reformulated OxyContin® was marketed relative to before. These findings are counter to findings in Purdue's three formal studies of abuse (that is, the NAVIPPRO™ Investigation, RADARS® System Poison Center Program Investigation, and the National Poison Data System [NPDS] Investigation). Unlike the planned analyses for the three formal studies of abuse, the CTS Investigation is limited by:

- the short postmarketing time frame used to assess OxyContin® after reformulated OxyContin was marketed
- the inability to assess reformulated OxyContin® specifically, or other specific formulations of ER oxycodone
- lack of adjustment for the availability of OxyContin®

In the Reviewer's opinion, it is difficult to determine whether the changes, in terms of absolute differences, in the prevalence of OxyContin® abuse were clinically meaningful. The CTS Investigation found a statistically significant increase in the prevalence of OxyContin® abuse from 2.6% to 2.9% of substance abuse treatment clients after marketing of reformulated OxyContin®, whereas the NAVIPPRO™ Investigation found a statistically significant decrease in the prevalence of OxyContin® abuse from (b) (4) among a similar population. To provide some context, the number of clients admitted to publicly-funded treatment centers in year 2010 was approximately (b) (4) so a (b) (4) absolute difference in the prevalence of OxyContin® abuse could correspond to approximately (b) (4) clients abusing (or not abusing)

Reference ID: 3292377

OxyContin®. This number of clients seems small relative to all clients entering substance abuse treatment. However, it is important to note that, if changes in the prevalence of OxyContin® abuse among clients entering substance abuse treatment correlate well with changes in the prevalence of OxyContin® abuse among persons who do not enter treatment, then the population-level changes in the prevalence of OxyContin® abuse, as potentially indicated by these two investigations, could be substantial and clinically meaningful.

The CTS Investigation assesses a possible measure of the desirability of OxyContin® for non-oral abuse: non-oral usual routes of administration. Prevalence of route-specific abuse, which is assessed in the NAVIPPRO™ Investigation, is a crude proxy measure of the desirability of OxyContin® abuse via non-oral routes of administration. That is, prevalence of route-specific abuse does not answer whether attempts to gain euphoria from non-oral OxyContin® abuse was successful, so a high prevalence may reflect many failed attempts at a euphoric response via non-oral abuse. For the same reason, the percent of clients reporting non-oral abuse among clients abusing a specific opioid is also a crude measure of the desirability of OxyContin® abuse via non-oral routes. On the other hand, if respondents report usually abusing an opioid via non-oral routes, then it is likely that they received a euphoric response from non-oral opioid abuse.

The CTS Investigation could have assessed the number of days of abuse in the past 30-days – another possible measure of the desirability of OxyContin® for abuse – but did not do so.

The RTI-NSDUH investigation found that the prevalence of non-medical OxyContin® use did not change in a statistically significant fashion. This finding is expected given that NSDUH is a survey of the general population and the reformulation of OxyContin® was designed to affect abuse via non-oral means, which are routes more common among experienced abusers. However, since NSDUH assesses non-medical use among the general population, changes in the prevalence of non-oral non-medical OxyContin® use among persons with more prescription opioid abuse experience may be masked by the larger general population with less or no opioid abuse experience.

5 CONCLUSION

Of all the investigations reviewed herein and prior, the Research Triangle Institute's (RTI) Client Treatment Study (CTS) Investigation is the only investigation to find statistically significant increases in the prevalence of OxyContin® abuse (from 2.6% to 2.9% of clients entering substance abuse treatment), and in the percent of persons abusing OxyContin® non-orally (from 44% to 48% of clients who abused OxyContin®). These findings are counter to findings in Purdue's three formal studies of abuse. In particular, the CTS Investigation's finding of increases in non-oral OxyContin® abuse contradicts the NAVIPPRO™ Investigation's finding of reductions in non-oral OxyContin® abuse. Meanwhile, the RTI-NSDUH Investigation did not find any statistically significant changes in non-medical OxyContin® use among a nationally representative sample of the general population.

Of the two updated analyses for Purdue's postmarketing study program, the ARGUS Investigation found statistically significant decreases in the number of spontaneous reports of fatalities reported to Purdue that were associated with extended-release oxycodone, but this decrease may reflect reporting biases inherent in passive surveillance. In addition, approximately 40% of fatal cases were not analyzed since they were missing dates of death. An updated analysis of the National Poison Data System Investigation found decreases in OxyContin®-related unintentional exposure calls to poison centers, but these decreases seemed to reflect the overall decrease in prescriptions dispensed for OxyContin®. Furthermore, Purdue has not

Reference ID: 3292377

presented any mechanistic or biological pathway that would explain the association between the reformulation of OxyContin® to decreases in unintentional exposures to OxyContin®.

In summary, among all findings from the investigations reviewed herein, only the CTS Investigation's finding of increases in non-oral OxyContin® abuse materially changes the conclusion of the interim report review, to which this review is an addendum. The interim report review concluded that "any decrease in OxyContin® abuse following the introduction of reformulated OxyContin® was mainly limited to non-oral routes of administration." The CTS's Investigation's findings on non-oral usual routes of administration runs counter to this conclusion, which now requires further qualification that increases in non-oral OxyContin® abuse have been observed in one investigation of clients admitted to substance abuse treatment, but not in another investigation assessing a similar population. Whether the reformulation of OxyContin® is associated with sustained increases or decreases in non-oral abuse can only be determined with more years of post-reformulation data on routes of abuse – ideally from both the NAVIPPRO™ Investigation and the CTS Investigation.

Reference ID: 3292377

6 APPENDIX A: REFERENCES

1. Novak, S. P. (2013). Comment in docket FDA-2013-D-0045. Research Triangle Institute International.

2. Purdue Pharma L.P. (2012). Report on the Findings as of December 2012 in Studies #10 and #11 of the 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) focusing on Fatal Events and Unintentional Exposures. Submitted to FDA on Dec 28, 2012, for NDA #022272: SDN 197 / eCTD 0165.

3. Trinidad, J., Dormitzer, C., & Kornegay, C. (2013). Review of "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". FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.

4. U.S.Department of Health and Human Services / Food and Drug Administration / Center for Drug Evaluation and Research. (2013). Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling (Draft Guidance).

5. Substance Abuse and Mental Health Services Administration and the Inter-University Consortium for Political and Social Research. (2013). Treatment Episode Data Set - Admissions (TEDS-A) Series. Retrieved on Feb 20, 2013, from http://www.icpsr.umich.edu/icpsrweb/SAMHDA/series/00056.

6. Lapteva, L. (2010). Regulatory History of Development of Abuse Deterrent Formulations. From the October 21-22, 2010 Meeting of the Anesthetic and Life Support Drugs Advisory Committee. FDA/CDER.

7. Butler, S. F., Black, R. A., Cassidy, T. A., Dailey, T. M., & Budman, S. H. (2011). Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm reduction journal, 8,* 29.

8. Snodgrass, J. & Holsinger, K. (2006). 2007 National Survey on Drug Use and Health: CAI Specifications for Programming English Version. Research Triangle Institute and Substance Abuse and Mental Health Services Administration.

Reference ID: 3292377

9. Brewer, T. & Colditz, G. A. (1999). Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA : the journal of the American Medical Association, 281,* 824-829.

10. Bronstein, A. C., Spyker, D. A., Cantilena, L. R., Jr., Green, J. L., Rumack, B. H., & Dart, R. C. (2011). 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clinical toxicology (Philadelphia, Pa.), 49,* 910-941.

11. Substance Abuse and Mental Health Services Administration. (2012). Substance Abuse Treatment Admissions by Primary Substance of Abuse, According to Sex, Age Group, Race, and Ethnicity, Year = 2010, UNITED STATES. Retrieved on Feb 25, 2013, from http://wwwdasis.samhsa.gov/webt/quicklink/US10.htm.

Reference ID: 3292377

7 APPENDIX B: ACRONYMS AND THEIR DEFINITIONS

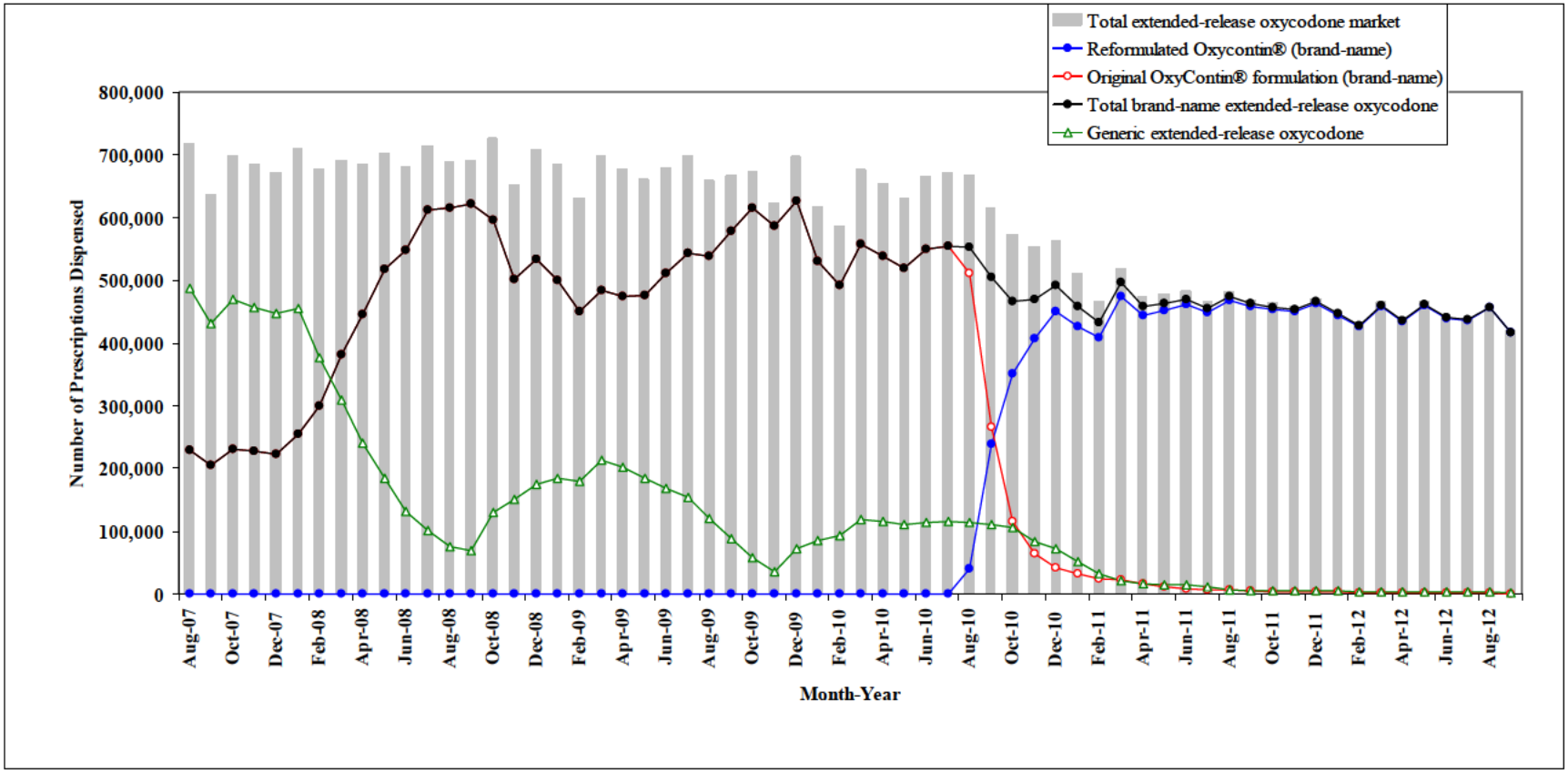
Table 7: List of Acronyms

Acronym	Definition
#QYYYY (such as 1Q2011)	First / second / third / fourth quarter of year YYYY
ARGUS	International Drug Safety Database
CTS	Client Treatment Study
ER	Extended-release
NAVIPPRO™	National Addiction Vigilance Intervention and Prevention Program
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
ORF	Reformulated OxyContin®
RADARS®	Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System
RTI	Research Triangle Institute
RTI-NSDUH	Research Triangle Institute's investigation using data from National Survey of Drug Use and Health
SAMHSA	Substance Abuse and Mental Health Services Administration
SE	Single-entity
TEDS	Treatment Episode Data Set

Reference ID: 3292377

8 APPENDIX C: DRUG UTILIZATION OF EXTENDED-RELEASE OXYCODONE, INCLUDING BRAND-NAME OXYCONTIN®

Figure 13: Number of generic and brand-name extended-release oxycodone prescriptions dispensed each month from August 2007 to August 2012



Data source: IMS Health, Vector One®: National (VONA), Extracted November 2012.

Reference ID: 3292377

9 APPENDIX D: EXPOSURE DEFINITIONS IN NPDS INVESTIGATION

Intentional exposures are defined as a purposeful action that results in an exposure. The following four categories relate to intentional exposures:

1. Intentional-Suspected suicidal: An exposure resulting from the inappropriate use of a substance for self-destructive or manipulative reasons. Cases included are suicides, suicide attempts, and suicide gestures, whether suspected or confirmed, cases in which history indicates patient was upset or depressed, patients who provide explanations for their actions such as "arguing with parents," "disturbed about poor grades," or "having marital problems", ingestions of large quantities of one or more drugs where the only likely explanation is the patient's intent to harm himself.
2. Intentional-Misuse: An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. Case included are a person deliberately mixes or applies a pesticide inappropriately so it will be more effective, a person deliberately increases the dosage of a medication to enhance its therapeutic effect, overuse of caffeine to study for an exam.
3. Intentional-Abuse: An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect. Recreational use of a substance for any effect should be coded here. Cases included are a person who inhales helium to talk funny, a person who uses GHB at a dance club, an infant with toxic effects or withdrawal symptoms as a result of the mother’s drug abuse while the child was in utero or while breast-feeding.
4. Intentional-Unknown: Exposure determined to be intentional but the specific motive is unknown.

Unintentional exposures are defined as an exposure that results from an unforeseen or unplanned event. For example, a child gaining access to a toxic substance, when it is obvious the child did not realize the danger of the action, is an unintentional exposure. The following eight coding options are available for unintentional exposures.

1. Unintentional-General: All unintended exposures that are not specifically defined below. Most unintentional exposures in children should be coded here. Cases include a toddler got into (and swallowed) a grandparent's prescription medicine, a bottle of drain opener left under the sink, or the entire contents of a container of chewable multivitamins.
2. Unintentional - Environmental: Any passive, non-occupational exposure that results from contamination of air, water or soil. Environmental exposures are usually, but not always, caused by human-made contaminants.
3. Unintentional-Occupational: Exposure that occurs as a direct result of the person being on the job or in the workplace.
4. Unintentional-Therapeutic error: An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only include medications or products substituted for medications. Drug interactions (or drug/food interactions) resulting from unintentional administration of drugs/foods which are known to interact are be included.
5. Unintentional-Misuse: Unintentional improper or incorrect use of a nonpharmaceutical substance. Unintentional misuse differs from intentional misuse in that the exposure was unplanned or not foreseen by the patient.

Reference ID: 3292377

6. Unintentional - Bite/sting: All animal bites and stings.
7. Unintentional - Food poisoning: All suspected or confirmed food poisoning exposures.
8. Unintentional - Unknown: An exposure determined to be unintentional but the exact reason is unknown.

Data Source: Section 4.11.2.1 of the interim report entitled "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011): November 2011 (Amended December 21, 2011)"

Reference ID: 3292377

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

/s/

JAMES TRINIDAD
04/12/2013

ELIZABETH M MALONEY
04/12/2013

JUDY A STAFFA
04/12/2013

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of an Interim Report and Related Abstracts

Date:	April 12, 2013
Reviewers:	James Phillip Trinidad, M.P.H., M.S., Regulatory Review Officer
	Division of Epidemiology II
	Catherine Dormitzer, Ph.D., M.P.H., Epidemiologist
	Division of Epidemiology II
	Cynthia Kornegay, Ph.D., Epidemiology Team Leader
	Division of Epidemiology II
Team Leader	Elizabeth Maloney, M.S., Dr.P.H., Epidemiology Team Leader
	Division of Epidemiology II
Division Director	Judy Staffa, Ph.D., R.Ph., Director
	Division of Epidemiology II
Drug Name:	OxyContin®
Subject	Review of "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"
Application Type/Number:	NDA 22-272; IND 29-038
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2012-2548

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

TABLE OF CONTENTS

EXECUTIVE SUMMARY 4
1 INTRODUCTION 10
1.1 Background 10
1.2 Regulatory History 10
2 REVIEW METHODS AND MATERIALS 10
3 REVIEW RESULTS 12
3.1 Overview of Methods and Preliminary Findings For Three Formal Studies 18
3.1.1 National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) 18
3.1.2 Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP) 62
3.1.3 National Poison Data System (NPDS) 78
3.2 Overview of Methods and Preliminary Findings for Eight Supplemental Investigations 87
3.2.1 National Surveys Investigation 87
3.2.2 Kaiser Permanente Health System Investigation 90
3.2.3 RADARS® System Drug Diversion Program Investigation 94
3.2.4 Doctor Shopping Investigation 101
3.2.5 Chat Rooms Investigation 106
3.2.6 Kentucky Investigation 108
3.2.7 IMS Xponent Investigation 111
3.2.8 International Drug Safety Database (ARGUS) Investigation 115
4 DISCUSSION 118
5 CONCLUSIONS 134
6 RECOMMENDATIONS TO THE SPONSOR 135
7 APPENDIX A: References 146
8 APPENDIX B: Acronyms and their definitions 153
9 APPENDIX C: Drug utilization of extended-release oxycodone, including brand-name OxyContin® 154
10 APPENDIX D: NAVIPPRO™ Investigation illustration of routes of abuse patterns for original and reformulated OxyContin® 156
11 APPENDIX E: Exposure definitions in RADARS® SPCP Investigation and NPDS Investigation 157
12 APPENDIX F: Extended-Release (ER) oxycodone formulations assessed by the RADARS® System Poison Center Program and the National Poison Data System (NPDS) 159
13 APPENDIX G: Case definitions in Kaiser Permanente Health System Investigation 162
14 APPENDIX H: MedDRA codes used in the ARGUS Investigation to identify relevant adverse event reports 164

Reference ID: 3292351

15 APPENDIX I: Non-systematic review of studies assessing the association between opioids with and without naloxone and opioid drug abuse 167

Reference ID: 3292351

EXECUTIVE SUMMARY

The Division of Epidemiology II reviewed an interim report submitted by Purdue Pharma L.P. Eleven investigations (including both formal studies of abuse and supplemental data) constitute Purdue's postmarketing study program.

As per the draft guidance on the evaluation and labeling of abuse-deterrent opioids, formal studies are designed to do all of the following:

- assess changes in outcomes that provide meaningful measures of abuse-deterrence
- produce nationally representative data or data from a large geographic region
- assess overall and route-specific abuse, misuse, or both abuse and misuse
- have sufficient data to assess changes in trend and level of OxyContin® abuse, misuse, or both abuse and misuse

Thus, these three formal studies' designs make them more informative than the other eight investigations for the assessment of the effect of the reformulation on OxyContin® abuse and misuse:

1. The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Investigation
2. The Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP) Investigation
3. National Poison Data System (NPDS) Investigation

Purdue has not presented data on the clinical outcomes of overdose and death from these formal studies of abuse.

I. The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Investigation

The NAVIPPRO™ Investigation, a cross-sectional prevalence study, assessed the prevalence of OxyContin® abuse in the past 30-days among adults entering a non-random sample of U.S. substance abuse treatment centers, based on standardized intake interviews that incorporated pill cards to identify medications. Route of administration and frequency of abuse (number of days of abuse) were also assessed.

The interim findings on prevalence of overall abuse among adults entering substance abuse treatment facilities who reported prescription opioid abuse were as follows:

- Prevalence of **any extended-release (ER) oxycodone** abuse decreased by (b) (4) from a prevalence of (b) (4) before marketing of reformulated OxyContin® to (b) (4) after marketing started for reformulated OxyContin®, and this relative percent difference was statistically significant.
- Prevalence of **other ER oxycodone abuse** (which includes generic ER oxycodone, Mexican and Canadian OxyContin®, and other ER oxycodone) decreased by (b) (4) from a prevalence of (b) (4) before to (b) (4) after marketing started for reformulated OxyContin®, and this relative percent was statistically significant.
- Prevalence of **all OxyContin®** abuse (U.S brand-name formulation only) decreased by (b) (4) from a prevalence of (b) (4) before to (b) (4) after marketing started for reformulated OxyContin®, and this relative percent was statistically significant.

Reference ID: 3292351

- Prevalences of **original OxyContin®** (b) (4)) and **reformulated OxyContin® (12.1%)** abuse were similar after marketing started for reformulated OxyContin®.
- The prevalence of reformulated OxyContin® abuse was 49% lower than the prevalence of original OxyContin® abuse before marketing started, a statistically significant finding.

Interim findings for route-specific abuse among adults entering substance abuse treatment facilities who reported prescription opioid abuse were as follows:

- Prevalence of **oral** abuse of **original** OxyContin® was **12.5% before**, and (b) (4) **after**, marketing started for reformulated OxyContin®.
- Prevalence of **oral** abuse of **reformulated OxyContin®** was **9.0%**.
- Prevalence of **non-oral** abuse of original OxyContin® was **18.1% before**, and (b) (4) **after**, marketing started for reformulated OxyContin®.
- Prevalence of **non-oral** abuse of **reformulated OxyContin®** was **4.8%.**

Abuse of reformulated OxyContin® was more oral, and less non-oral, than abuse of original OxyContin®. Among those who abused **original** OxyContin®, approximately **55%** reported abusing original OxyContin® via **oral** routes, and approximately **70%** reported abuse via **non-oral** routes. Meanwhile, among those who abused **reformulated** OxyContin®, approximately **75%** reported abusing reformulated OxyContin® via **oral** routes, and approximately **40%** reported abuse via **non-oral** routes.

Those who abused original OxyContin® abused it more frequently than those who abused reformulated OxyContin®. The average number of days of original OxyContin® abuse before the introduction of reformulated OxyContin® was 10.75 days in the past 30 days. The average number of days of reformulated OxyContin® abuse was 7.5 days.

The Office of Surveillance and Epidemiology concluded that continued prevalence of abuse of original OxyContin® and other ER oxycodone – after these products were withdrawn from commercial distribution – potentially confounds the prevalence of reformulated OxyContin® abuse, route specific abuse, and average number of days of abuse after marketing started for reformulated OxyContin®. At this time, the Office of Surveillance and Epidemiology cannot determine what the prevalence of reformulated OxyContin® abuse could be in the absence of abuse of original OxyContin® and other ER oxycodone. In addition, as could be expected by the notable declines in the prescriptions dispensed for generic ER oxycodone after marketing of reformulated OxyContin®, reductions in the prevalence of ER oxycodone abuse were mainly attributable to reductions in abuse of other ER oxycodone (which includes generic ER oxycodone), not OxyContin®.

II. The Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP) Investigation

The RADARS® SPCP Investigation, a cross-sectional study, uses data on exposure calls to a non-random sample of poison centers to assess changes in the number of OxyContin®-related intentional exposure (particularly, abuse-related intentional exposure cases). Exposure calls for generic ER oxycodone and ER oxycodone regardless of formulation were not assessed.

- The RADARS® SPCP Investigation observed a persistence in intentional abuse exposures for original OxyContin® after marketing started for reformulated OxyContin®.
- The RADARS® SPCP Investigation found a statistically significant (b) (4) reduction in the mean quarter-year number of intentional abuse exposures to OxyContin after marketing

Reference ID: 3292351

started for reformulated OxyContin®. Adjusted for the number of recipients dispensed OxyContin®, the reduction attenuated to 32%, but was still statistically significant.

III. National Poison Data System (NPDS) Investigation

The NPDS Investigation, a cross-sectional study, uses data on exposure calls to **all** U.S. poison centers to assess changes in the number of OxyContin®-related intentional exposures (particularly, intentional abuse and intentional misuse exposures). Exposure calls for generic ER oxycodone and ER oxycodone regardless of formulation were not assessed.

- Similar to the RADARS® SPCP Investigation, the NPDS Investigation found a 30% reduction in the quarter-year average number of OxyContin®-related intentional abuse exposure cases.
- The NPDS Investigation also found a (b) (4) reduction in the quarter-year average number of OxyContin®-related intentional misuse exposure cases.

None of the other eight investigations in Purdue's postmarketing portfolio suggest an increase in OxyContin® abuse after marketing started for reformulated OxyContin®:

IV. Kaiser Permanente Investigation

The Kaiser Permanente Investigation, a cohort study, uses administrative claims data to estimate and compare rates of opioid overdose and poisoning events among patients prescribed OxyContin® and comparator opioids. This investigation is currently in its outcome validation phase.

V. The RADARS® System Drug Diversion Investigation

The RADARS Drug Diversion Investigation, a pre-post descriptive investigation, uses data collected from law enforcement agencies to assess changes in the number of drug diversion cases and street prices for OxyContin®. This investigation found statistically significant reductions in the quarter-year average number of OxyContin®-related diversion cases, as well as a statistically significantly lower average street price for reformulated OxyContin® than for original OxyContin®. Although drug diversion cases and street prices could be a surrogate measure of drug desirability for abuse, there is no information on the supply of diverted OxyContin®, so these findings cannot be placed in a complete context. In addition, the interim report did not present any measure of the amount of OxyContin® caught in drug diversion cases. Lastly, analysis of street prices did not account for the fact that the number of 80 mg tablets dispensed – the highest dose for OxyContin® - decreased after marketing started for reformulated OxyContin®.

VI. Doctor Shopping Investigation

The Doctor Shopping Investigation, a cross-sectional study, uses data from prescription drug monitoring programs and IMS LRx (a longitudinal database of person-level prescription data) to characterize and compare counts and rates of doctor-shopping. This investigation found that reductions in potential OxyContin® doctor-shopping were more pronounced among the subgroups of cash payers, younger patients, and those who used OxyContin® before marketing started for reformulated OxyContin®. At this time, there are no validation studies on the doctor-shopping algorithms used in this study, so it cannot be determined from this study whether the

Reference ID: 3292351

algorithms truly measure doctor-shopping or a possible surrogate measure for clinical outcomes of interest (addiction, overdose, or death).

VII. Chat Rooms Investigation

The Chat Rooms Investigation qualitatively analyzes data from internet forums related to drug abuse. This investigation found that the proportion of OxyContin® posts on routes of administration and extraction statistically significantly decreased during the study period after marketing started for reformulated OxyContin®, but the proportion of posts with an abuse-endorsing or abuse-discouraging endorsement did not change. It is unclear how to interpret these findings since findings for the baseline period (August 2008 – August 2010) were not presented, and there were a large percentage of posts with 'mixed' and 'unclear' endorsement.

VIII. The Kentucky Investigation

The Kentucky Investigation, a cross-sectional study, uses interviewer-administered survey data of respondents in Perry County, KY, all who abused reformulated OxyContin® prior to the introduction of reformulated OxyContin®. This investigation found that the percent of respondents reporting reformulated OxyContin® abuse was lower than the percent of respondents reporting abuse of original OxyContin®, and the frequency of reformulated OxyContin® abuse was also lower than the frequency of original OxyContin® abuse. These results are not national generalizable because they are based on a very small, geographically restricted sample.

IX. The IMS Xponent Investigation

The IMS Xponent Investigation, a drug utilization study, uses nationally representative drug use data to assess changes in prescriptions dispensed for OxyContin®. This investigation found that, although the monthly average number of OxyContin® prescriptions dispensed nationwide only declined slightly, the greatest declines were among the prescriptions paid for with cash, 40 and 80 mg strengths, and those prescriptions written by prescribers whose prescribing practices are indicative of abuse and diversion. Although these findings may reflect, among other things, a reduction in the demand for OxyContin® for abuse or misuse, exactly how changes in prescribing patterns correspond to changes in behavioral or clinical outcomes is unclear. In particular, the Risk Evaluation and Mitigation Strategy introduced specifically for reformulated OxyContin® could have been influencing prescribing patterns.

X. The International Drug Safety Database (ARGUS)

The International Drug Safety Database (ARGUS) uses spontaneous report data collected by Purdue to assess drug abuse, intentional drug misuse, overdose, and medication errors associated with both OxyContin® formulations. Investigation found that the number of spontaneous reporting cases associated with drug abuse, overdose, and medication error / maladministration were consistently lower for reformulated OxyContin® than for original OxyContin®. Furthermore, analyses on 344 fatal OxyContin® cases that had information on dates of death found that the number of fatal cases declined after the marketing started for reformulated OxyContin®; however, it is unclear if these reductions are biased by missing data, particularly since 409 case reports of the total 753 case reports did not contain dates of death and were subsequently removed from analysis. Since the ARGUS data represent passive surveillance, the changes observed may be the result of other factors that affect reporting and interpretation of case

Reference ID: 3292351

reports, such as underreporting, missing information, inability to assess causality, recall bias, and confounding.

XI. National Surveys Investigation

The National Surveys Investigation, a cross-sectional study, uses survey data from the National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), and RADARS® System College Survey. The general aim of this investigation is to assess prevalence of OxyContin® abuse among students (MTF and RADARS® System College Survey) and the general population (NSDUH). The interim report did not present findings from NSDUH. This investigation found no difference in the prevalence of non-medical OxyContin® use among children and college students.

Conclusions

Preliminary findings from several of the above investigations are suggestive of reductions in OxyContin® abuse after the introduction of reformulated OxyContin® to the market. In particular, the NAVIPPRO™ Investigation, the only formal study of abuse to directly compare prevalence of OxyContin® abuse between formulations, found a lower prevalence of reformulated OxyContin® abuse; however, this finding does not provide definitive evidence of abuse-deterrence as it is confounded by the persistence in abuse of original OxyContin® and, possibly generic ER oxycodone, even though commercial distribution of these original ER oxycodone products ceased. That is, under the assumption that the original and reformulated ER oxycodone formulations are equally substitutable for abuse, confounding is likely to occur when abuse of brand or generic original ER oxycodone (confounder) is inversely associated with abuse of reformulated OxyContin® and, therefore, could partially or totally explain the observed lower levels of reformulated OxyContin® abuse. As explained by this potential confounding, it is possible that lower prevalence of reformulated OxyContin® abuse may simply reflect persisting prevalence of abuse of original formulations of ER oxycodone after marketing of reformulated OxyContin®.

The inherent assumption in pre-post analyses of OxyContin® abuse is that, following the introduction of reformulated OxyContin® to the market, brand and generic original formulations of ER oxycodone were not available for abuse after a reasonable transition period. This assumption was violated in all investigations. Even though commercial distribution of these products ended, abuse of brand and generic original formulations of ER oxycodone continued after reformulated OxyContin® was marketed. There are several possible explanations for continued abuse of original ER oxycodone, including misclassification of reformulated OxyContin® abuse as original ER oxycodone abuse; misclassification of original ER oxycodone abuse as reformulated OxyContin® abuse is also possible. Whether less abuse of reformulated OxyContin® - or OxyContin® regardless of formulation - will be sustained after licit and illicit supplies of original formulations of ER oxycodone are exhausted is not known at this time.

Whether the reformulation of OxyContin® resulted in a decrease in abuse-related clinical outcomes has not been demonstrated. Data on the clinical outcomes of overdose and death has not been presented for the formal studies; the Kaiser Permanente Investigation aims to assess overdose and poisonings, but is in its outcome validation stage; and the ARGUS Investigation's findings on overdose and mortality could be biased by factors (such as, missing data) that affect reporting and interpretation of cases collected by Purdue.

Reference ID: 3292351

In addition, any decrease in OxyContin® abuse following the introduction of reformulated OxyContin® was mainly limited to non-oral routes of administration, a finding that was primarily supported by one investigation: the NAVIPPRO™ Investigation. Finding that non-oral abuse of the reformulation was lower than the original formulation is particularly important since the reformulation of OxyContin® was specifically designed to deter certain non-oral routes of abuse.

The NAVIPPRO™ Investigation contains the most suggestive evidence that reformulating OxyContin® has deterred abuse, particularly via non-oral routes of administration. However, it is unknown if the NAVIPPRO™ Investigation results will be robust after this investigation adjusts for availability of each extended-release (ER) oxycodone formulation, which is important given that all ER oxycodone formulations – both brand and generic – were all abused after marketing started for reformulated OxyContin®. In addition, the available data presented for the NAVIPPRO™ Investigation do not adequately explain the persistence of original OxyContin® abuse, which the RADARS® SPCP Investigation also observed.

Overall, whether or not the reformulation of OxyContin® resulted in a decrease in OxyContin® abuse – and related clinical outcomes – cannot be determined at this time:

- Purdue's study program's findings on overall and route-specific prevalence of reformulated OxyContin® abuse, as well as number of days of abuse, are confounded by the persistence of abuse of original OxyContin® and, possibly, other ER oxycodone
- The postmarketing study program needs more data (that is, longer follow-up) Purdue has not provided any robust data on the clinical outcomes of overdose, poisoning, and death, and the rates of addiction have not been formally assessed.

Furthermore, whether changes in the route of administration profile can help predict population rates of overdose, poisonings, addiction, and death cannot be determined at this time because persons who abuse opioids via non-oral routes are more likely to be experienced with prescription opioid abuse.

Each investigation in Purdue's postmarketing study program could be stronger if it was not missing one or more characteristics allowing for a better assessment of OxyContin® abuse. For this reason, Purdue's postmarketing study program uses a 'mosaic' approach to address the postmarketing requirement required by FDA. That is, each investigation aims to provide a strength (or different perspective) that complements the weaknesses of other investigations. However, the interim report was <u>not</u> formatted in a way that allowed the eight additional investigations containing supplemental data to provide context and support for the findings from the three formal studies of abuse.

In summary, the interim report included no more than approximately 1.5 years of postmarketing data for reformulated OxyContin®. The Office of Surveillance and Epidemiology / Division of Epidemiology II recommends at least 3 to 5 years of postmarketing data to assess whether the reformulation of OxyContin® deters abuse and helps prevent abuse-related clinical outcomes. In particular, longer follow-up is needed for Purdue's postmarketing study program to evaluate the persistence of original OxyContin® abuse, and also to allow Purdue to complete planned assessments and analyses of clinical outcomes.

Reference ID: 3292351

1 INTRODUCTION

1.1 BACKGROUND

The Division of Anesthesia, Analgesia, and Addiction Products consulted the Division of Epidemiology II, requesting that the Division of Epidemiology II review an interim report submitted by Purdue Pharma L.P. The Division of Epidemiology II also reviewed abstracts that complemented data from the interim report.

Appendix B lists all the acronyms used in this review.

1.2 REGULATORY HISTORY

Reformulated OxyContin® is a single-entity (SE) extended-release (ER) opioid developed by Purdue Pharma L.P. Reformulated OxyContin® was approved for marketing in the U.S. on April 5, 2010. Reformulated OxyContin® replaced the original OxyContin® formulation, which was approved on December 12, 1995. Specifically, on August 5, 2010, Purdue stopped shipping original OxyContin® tablets to pharmacies, and on August 9, 2010, Purdue started shipping only reformulated OxyContin® tablets to pharmacies. However, pharmacies still dispensed their remaining stock of original OxyContin® after August 5, 2010.

Both formulations are indicated for the "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time" (1; 2). Compared to the original formulation, reformulated OxyContin® is more resistant to tampering, specifically, dissolving in liquids, breaking, crushing, or chewing.

Purdue hypothesized that the reformulation of OxyContin® would reduce abuse via injection and snorting, and possibly via oral routes that involve breaking, crushing, or chewing. The postmarketing requirement in the NDA Approval Letter for reformulated OxyContin® states that Purdue must assess the following (3):

> *"…the known serious risks of [reformulated OxyContin®], in particular, whether the changes made to [OxyContin®] that are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences…addiction, overdose, and death."*

On July 31, 2012, FDA received an interim report of Purdue's postmarketing study program that aims to assess the effects of the reformulation on OxyContin® abuse. This interim report was an update of the December 2011 interim report for the 11 investigations that constitute Purdue's postmarketing study program.

2 REVIEW METHODS AND MATERIALS

The materials reviewed herein included interim reports for Purdue's postmarketing study program, proposed study protocols, and related communications between FDA and Purdue Pharma L.P. (4-28):

- Purdue Pharma L.P. (2012). 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),

Reference ID: 3292351

Patient Adverse Events, and Unintentional Exposures. Submitted to FDA on July 31, 2012, for NDA #022272: SDN 171 / eCTD 0143

- Mathers, P.R. & Davidson, J.A. (2012). Citizen Petition, document 0001 of docket FDA-2012-P-0760. Kleinfeld, Kaplan, and Becker, L.L.P. *on behalf of* Purdue Pharma, L.P. Submitted to FDA on July 18, 2012, for NDA #022272: SDN 167 / eCTD 0140
- Purdue Pharma L.P. (2011). A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011). Amended December 21, 2011. Submitted to FDA on December 23, 2011, for NDA# 022272: SDN 89 / eCTD 0088
- Purdue Pharma L.P. (2011). Post-marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death. Submitted to FDA on January 26, 2011, for NDA# 022272: SDN 89 / eCTD 0088
- General Advice Letters sent from FDA to Purdue, dated December 21, 2010; April 5, 2011; May 19, 2011; and May 24, 2011
- Purdue's responses to FDA's General Advice Letters, dated January 26, 2011, and December 1, 2011 (SDN 89 / eCTD 0088 and SDN 140 / eCTD 0119, respectively)
- Purdue's responses to FDA's Information Request, dated October 1, 2012; October 4; 2012;, October 22, 2012; November 30, 2012; December 20, 2012; and February 20, 2013 (SDN 181 / eCTD 0153, SDN 182 / eCTD 0154, SDN 188 / eCTD 0157, SDN 190 / eCTD 0160, SDN 194 / eCTD 0164, and SDN 201 / eCTD 0170, respectively)
- Purdue's submissions collectively containing 44 abstracts, which are based on the post-marketing epidemiology study program, being presented at various conferences between September 2011 and June 2013 (SDN 105 / eCTD 0104, SDN 151 / eCTD 0129, SDN 156 / eCTD 0133, SDN 158 / eCTD 0135, SDN 169 / eCTD 0134, SDN 175 / eCTD 0146, SDN 177 / eCTD 0149, SDN 183 / eCTD 0156, and SDN 193 / eCTD 0162)

To provide context for the current review, the following FDA evaluations were also reviewed (29-37):

- Evaluation of Preliminary Proposals and Presentations of Abuse Deterrent Studies for Extended Release OxyContin® and Embeda®, by Cynthia Kornegay, dated November 24, 2010
- Statistical Review and Evaluation of Oxycontin (oxycodone hydrochloride), by Bradley McEvoy, dated May 4, 2011
- Evaluation of Protocol of Abuse-Deterrence Studies, by Cynthia Kornegay, dated March 17, 2011
- Evaluation of Six Protocols for Abuse-Deterrence Studies on Continued Release OxyContin, by Cynthia Kornegay, dated May 13, 2011
- Review of "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011)," by James Phillip Trinidad and Catherine Dormitzer, dated April 27, 2012
- Statistical Review and Evaluation, by Eric Frimpong, dated October 5, 2012

Reference ID: 3292351

- Statistical Review and Evaluation, by Rongmei Zhang, dated November 1, 2012
- Statistical Review and Evaluation, by Rongmei Zhang, dated March 19, 2013
- Statistical Review and Evaluation, by Yu-te Wu, dated February 22, 2013

Appendix A lists all the references cited in this review.

3 REVIEW RESULTS

In July 2012, Purdue submitted interim findings for 11 investigations. Eight of these investigations had methods described in the protocols submitted to FDA on January 26, 2011. Ten of these investigations contain findings that have been updated since the interim report submitted to FDA on December 23, 2011.

Although the abstracts had analyses that differed slightly from those presented in the July 2012 interim report, review of these abstracts did not substantially change the results of this review, except where noted.

The basic design for the 11 investigations is a comparison of OxyContin® abuse before versus after marketing of reformulated OxyContin®, and a comparison of changes in OxyContin® abuse to changes in abuse of comparator opioids.

Three of these investigations are formal[a] studies whose design makes them more informative than the other eight investigations for assessing the effect of the reformulation on OxyContin® abuse and misuse. As per the draft guidance on the evaluation and labeling of abuse-deterrent opioids (38), the three formal studies of abuse are designed to do all of the following:

- assess changes in outcomes that provide meaningful measures of abuse-deterrence
- produce nationally representative data or data from a large geographic region
- assess overall and route-specific abuse, misuse, or both abuse and misuse
- have sufficient data to assess changes in trend and level of OxyContin® abuse, misuse, or both abuse and misuse

These formal studies, whose methods and preliminary findings are described in more detail in Section 3.1, use data from the following data sources:

- National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™)
- Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP)
- National Poison Data System (NPDS)

Of the three formal studies, only the NAVIPPRO™ Study assessed changes in abuse by both oral and non-oral routes of administration. For this reason, this review will focus more attention on

[a] The FDA review of the Dec 2011 Interim Report stated that these studies were pivotal, not formal studies of abuse. This wording has been changed to emphasize that certain studies are more methodologically focused than other studies to study abuse and abuse-related clinical outcomes, not that they will produce results suggestive of being 'pivotal.' For more information on formal studies of abuse, refer to the Draft Guidance for Industry on Evaluation and Labeling of Abuse-Deterrent Opioids (38).

Reference ID: 3292351

the NAVIPPRO™ study than the other investigations that constitute Purdue's postmarketing study program.

The formal studies' designs and interim findings are summarized in Table 1.

A review of a previous interim report also considered the Kaiser Permanente Study as a formal study of abuse. However, further review of this study's definition of abuse suggests that this study does not meet the criteria for consideration as a formal study of abuse (see Section 3.2.2 of this review).

Section 3.2 describes methods and findings for eight other investigations that supplement the three formal studies with additional context on societal, behavioral, and clinical aspects of OxyContin® abuse. These supplemental investigations use data from the following data sources:

- Three national surveys – National Survey on Drug Use and Health, Monitoring the Future, and RADARS® System College Survey
- Kaiser Permanente Health System
- RADARS® System Drug Diversion Program
- Prescription drug monitoring programs and IMS LRx
- Internet chat rooms
- Surveys conducted in rural Kentucky
- IMS Xponent
- Purdue's International Drug Safety Database (ARGUS).

The supplemental investigations' designs and interim findings are summarized in Table 2.

Reference ID: 3292351

Table 1: Summary[†] of three formal studies aiming to assess the effect of the reformulation of OxyContin® on OxyContin® abuse and misuse

Study	Objective	Population	Study periods, relative to marketing of reformulated OxyContin	Opioid exposures	Routes of abuse	Measure and corresponding statistical analysis	Primary findings
NAVIPPRO™	- To compare the proportion of adults reporting past 30-day OxyContin® abuse via any route of administration before/after marketing started - To compare the proportion of those abusing OxyContin® by alternate routes of administration before/after marketing started for reformulated OxyContin® - To compare the change in the proportion of individuals abusing OxyContin® via specific alternative routes of administration before/after marketing started - To compare the average number of days in the past 30 days which OxyContin® was abused, before/after marketing started	Adults entering substance abuse treatment centers	**Before**: Jul 1, 2009 – Aug 8, 2010 **After**: Aug 9, 2010 – Mar 1, 2012	- Original OxyContin® - Reformulated OxyContin® - OxyContin® regardless of formulation - ER oxymorphone - ER morphine	- Any route - Any oral route - Any non-oral route - Injection - Snorting - Smoking	**Prevalence and rates of reported drug abuse -** generalized linear mixed models **Frequency of reported drug abuse -** generalized log-binomial models	- Prevalence of overall abuse was (b) (4) for original OxyContin® before marketing started for reformulated OxyContin®, and (b) (4) for reformulated OxyContin®. - Average frequency of abuse was 10.6 days in the past 30 days for original OxyContin®, and 7.5 days for reformulated OxyContin®. - Oral and non-oral abuse of reformulated OxyContin® was statistically significantly lower than oral and non-oral abuse of original OxyContin®.
RADARS® SPCP	- To estimate and compare the change in the number of intentional exposure cases for OxyContin® and opioid comparators, before/after marketing started for reformulated OxyContin®	U.S. poison control center cases	**Before**: 4Q2008-3Q2010 **After**: 4Q2010-1Q2012	- OxyContin® regardless of formulation - IR SE oxycodone - Other prescription opioids[α]	Any route (no specific routes assessed)	**Intentional abuse exposures -** negative binomial regression	Quarter-year population-adjusted average number of intentional abuse exposure cases associated with OxyContin® was (b) (4) lower after marketing started for reformulated OxyContin®.
NPDS	- To assess changes in exposures – according to calls made to U.S. poison centers – associated with OxyContin® and other opioids before and after marketing started for reformulated OxyContin®	U.S. poison control center cases	**Before**: 3Q2009-2Q2010 **After**: 4Q2010-4Q2011	- OxyContin® regardless of formulation - Other SE oxycodone prescription products[β] - Heroin	Any route (no specific routes assessed)	**Intentional abuse and intentional misuse exposures** – descriptive statistics only	Quarter-year average number of intentional abuse and intentional misuse exposure cases associated with OxyContin® decreased 30% and (b) (4), respectively, after marketing started for reformulated OxyContin®.

[†]Summary includes only details pertinent to primary findings from the interim report

[α]IR oxycodone products, hydrocodone, fentanyl, hydromorphone, morphine, oxymorphone, methadone, buprenorphine, tramadol, and tapentadol

[β]Excludes OxyContin®, but includes generic ER oxycodone

Reference ID: 3292351

Table 2: Summary[†] of eight supplemental investigations aiming to assess the effect of the reformulation of OxyContin® on OxyContin® abuse and misuse

Investigation	Objective	Population	Study periods, relative to marketing of reformulated OxyContin	Opioid exposures	Routes of abuse	Measure and corresponding statistical analysis	Primary findings
National Surveys	To estimate prevalence of and changes in the prevalence of use of OxyContin® and other opioids for non-medical purposes before/after marketing started for reformulated OxyContin®	Monitoring the Future 8th, 10th, and 12th graders RADARS® System College Survey College students	**Before**: Aug 2004 – Aug 2010 **After**: Aug 2010 – Aug 2012	Monitoring the Future OxyContin® RADARS® System College Survey - OxyContin® regardless of formulation - IR oxycodone prescription products - Other prescription opioids[α]	Any (no specific routes assessed)	**Prevalence of reported non-medical drug use** - negative binomial regression	Both the Monitoring the Future Survey and RADARS® System College Survey found that prevalence of non-medical OxyContin® use did not change after marketing started for reformulated OxyContin®.
Kaiser Permanente (KP) Health System	To estimate and compare rates of opioid overdose and poisoning events among patients prescribed OxyContin® and comparator opioids, and among patients not prescribed these opioids, before and after marketing started for reformulated OxyContin®	Members in the KP Northwest and KP Northern California Health Systems	For validation stage: 2H2008 – 1H2012	- ER oxycodone - Other opioids	Any (no specific routes assessed)	**Opioid overdose and poisonings** - descriptive statistics only	Validation stage found that case definition for opioid overdose was neither specific or sensitive for overdose events
RADARS® System Drug Diversion Program	- To compare the change in the number of drug diversion cases associated with OxyContin® versus opioid comparators, occurring before/after marketing started for reformulated OxyContin® - To compare the change in the average street price of OxyContin® versus opioid comparators, occurring before/after marketing started for reformulated OxyContin®	U.S.	**Before**: 3Q2009-3Q2010 **After**: 4Q2010-1Q2012	- OxyContin® - Other prescription opioids - IR SE oxycodone prescription products	Not applicable	**Drug diversion cases -** negative binomial regression **Street prices -** formal statistical analysis not described	- Number of diversion cases associated with either OxyContin® or other prescription opioids decreased after marketing started for reformulated OxyContin® - The average population-adjusted rate of diversion cases associated with OxyContin® during 3Q2009-3Q2010, the population-adjusted rate of diversion cases associated with OxyContin® was lower most quarter-years from 4Q2010 to 1Q2012

Reference ID: 3292351

Doctor-Shopping	To characterize and compare the counts and rates of doctor-shopping for OxyContin® and opioid comparators before/after marketing started for reformulated OxyContin®	Ohio analyses: Patients who had prescriptions dispensed in Ohio IMS LRx analyses: Patients who had prescriptions dispensed in the U.S.	For Ohio analyses: **Before**: 1H2009-2H2010 **After**: 1H2011 For IMS LRx analyses: **Before**: 2H2009 – 1H 2010 **After**: 1H2011-2H2011	OxyContin®	Not applicable	**Individuals doctor-shopping for OxyContin®** - formal statistical analysis not described	From Ohio analyses More specific definitions of doctor-shopping (4+ prescribers / 4+ pharmacies) showed reductions in potential doctor-shopping. From IMS LRx analyses Reductions in the percent of OxyContin® users who are potentially doctor-shopping for OxyContin® were more pronounced among patients paying at least once by cash, younger patients, and patients who had filled OxyContin® within the three months prior to the start of each 6-month study period
Chat Rooms	To characterize and assess trends in the amount and nature of online discussions regarding reformulated OxyContin® and opioids comparators, before/after marketing started for reformulated OxyContin®	Authors of posts from selected internet forums related to opioid abuse	**After**: Aug 2008 – Aug 2010	- OxyContin® - Vicodin® - Dilaudid®	As reported by chat room authors	**Amount and nature of online discussions** – formal statistical analysis not described	- Proportion of posts for the topic categories of routes of administration and extraction methods were statistically significantly lower in July 2011 through September 2011 than in January 2011 through March 2011. - Proportion and pattern of endorsing, discouraging, and non-abuse related posts were unchanged for reformulated OxyContin® and the comparators between the period June 2010 – September 2011 and the period November 2010 – January 2011.
Kentucky	To collect quantitative and qualitative data to determine the extent to which drug use patterns change following introduction of reformulated OxyContin®	Survey respondents in Appalachian Perry County, KY	**Before: Aug 2010** **After**: Dec 2010 – Sep 2011	- Original OxyContin® - Reformulated OxyContin® - Other drugs[β]	- Any - Swallowing - Chewing - Snorting - Injection - Drinking	**Percent reporting opioid-specific drug abuse** - formal statistical analysis not described	- Percent of respondents reporting reformulated OxyContin® abuse after marketing started for reformulated OxyContin® was lower than the percent of respondents reporting abuse of original OxyContin® before marketing started for reformulated OxyContin®. - Respondents reported abusing reformulated OxyContin® less frequently than abuse of original OxyContin® in August 2010.

Reference ID: 3292351

IMS Xponent	- To assess changes in opioid prescribing among selected groups of prescribers, before/after marketing started for reformulated OxyContin® - To estimate changes in the prescribing of higher versus lower strengths of OxyContin®, before/after marketing started for reformulated OxyContin® - To estimate the extent of reductions in OxyContin® prescribing due to Abuse and Diversion Detection (ADD) prescribers - To estimate changes in the number of OxyContin® prescriptions paid for by cash, before/after marketing started for reformulated OxyContin®	- All prescribers in U.S. - ADD prescribers - Non-ADD prescribers	**Before:** Aug 2009 – Jul 2010 **Transition and after transition**: Aug 2010 – Jul 2011	- OxyContin® - Other prescription opioids[γ]	Not applicable	**Prescribing patterns** - descriptive statistics only	- The monthly average number of OxyContin® prescriptions dispensed slightly declined nationwide after marketing started for reformulated OxyContin® - The greatest declines were among OxyContin® prescriptions prescribed by ADD prescribers, being 40 mg or 80 mg strengths, or paid for with cash
ARGUS	To assess changes in the number of adverse event reports reported to Purdue and associated with OxyContin®, before/after marketing started for reformulated OxyContin®	U.S.	**Before:** Jan 2010 – Dec 2010 **After:** Jan 2011 – Dec 2011	- Original OxyContin® - Reformulated OxyContin®	As reported to Purdue	**Adverse event reports** - descriptive statistics only	The number of cases associated with drug abuse, overdose, and medication error/maladministration was consistently lower for reformulated OxyContin® than for original OxyContin®

[†]Summary includes only details pertinent to primary findings from the interim report

[α]Oxycodone, hydrocodone, buprenorphine, fentanyl, morphine, hydromorphone, and methadone

[β]Alcohol, heroin, methadone, other oxycodone, hydrocodone, hydromorphone, fentanyl, benzodiazepines, cocaine, crack cocaine, methamphetamine, marijuana

[γ]ER hydromorphone, ER morphine, ER oxymorphone, generic ER oxycodone, IR hydromorphone, SE IR oxycodone, methadone

Reference ID: 3292351

3.1 OVERVIEW OF METHODS AND PRELIMINARY FINDINGS FOR THREE FORMAL STUDIES

3.1.1 National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™)

Data source/data collection

The NAVIPPRO™ Investigation collects product-specific data from adults entering a non-random sample of substance abuse treatment centers.

This investigation uses data from two computerized, NAVIPPRO™ patient assessment tools:

- Addiction Severity Index – Multimedia Version (ASI-MV®)
- Comprehensive Health Assessment for Teens (CHAT™)

According to the protocol, this investigation will analyze data from the ASI-MV® and CHAT™ data streams separately. The interim report contains findings from only the ASI-MV® data stream. Because the interim report does not contain findings from the CHAT™ data stream, there is no further reference to the CHAT™ investigation component in this review.

In the Reviewer's opinion, ASI-MV® data is likely generalizable to adults entering substance abuse treatment. This data stream includes a convenience sample of 500 privately and publicly funded substance abuse treatment centers located in over 35 states throughout the U.S. Although it is not clear how treatment centers determine whether to use the ASI-MV® assessment tool, the ASI-MV® data have been shown to be similar with respect to gender, age, and education characteristics to patients captured by the Substance Abuse and Mental Health Services Administration's (SAMHSA) Treatment Episode Data Set (TEDS) (12). The ASI-MV® data capture more Hispanic individuals and employed individuals than TEDS. These differences are likely attributable to the fact that ASI-MV® collects data from both publicly and privately funded centers, whereas TEDS only collects data for publicly funded centers.

Adults self-administer the ASI-MV® during their intake interview at substance abuse treatment centers. ASI-MV® assesses substance use in the past 30 days, including specific prescription drugs. ASI-MV® also assesses severity of a range of problems typically associated with substance abuse, such as, alcohol and drug use, medical status, employment, psychiatric status.

The ASI-MV® gathers specific information on drug abuse, including

- what drugs have been abused in the past 30-days
- what routes of administration were used to abuse each drug
- how many days in the past 30 days each drug was abused

Figure 1 illustrates the ASI-MV® visuals that help respondents identify which drugs (such as OxyContin®) and formulations of those drugs (such as original or reformulated OxyContin®) they abused. In addition, ASI-MV® provides trade, generic, and street names to help respondents identify the drugs they abused. Furthermore, when respondents indicate that they abused OxyContin®, an alert window reminds them to review the OxyContin® formulations' images/indicia. This alert window aims to ensure accurate identification of the formulation that respondents abused.

Reference ID: 3292351

Figure 1: The Addiction Severity Index – Multimedia Version helps respondents identify drugs that they abused, including the specific drug formulations they abused

(b) (4)

Data Source: Figure 3 of the protocol entitled "Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death"

Treatment centers participating in the NAVIPPRO™ surveillance system did not uniformly update the ASI-MV® with the software update that enables identification of reformulated OxyContin® and OxyContin® from Canada and Mexico. Still, the NAVIPPRO™ surveillance system was able to immediately identify when each treatment center applied the software update.

Purdue asserts that, while the possibility of misclassification of various ER oxycodone products cannot be ruled out, misclassification is unlikely to result in biased estimates of rates of OxyContin® abuse before versus after marketing started for reformulated OxyContin®. According to Purdue, the following statements support the above assertion:

- The computer-assisted visual guidance provided by ASI-MV® aims to increase accuracy of drug identification.
- There is anecdotal evidence of awareness of specific formulations among people who abuse OxyContin®.
- Examination of the route of administration profile for original OxyContin® abuse was similar before and after marketing started for reformulated OxyContin®.

These statements do not address how misclassification (if present) could bias NAVIPPRO™ Investigation findings and the possible direction and extent of that bias. The sub-section "Preliminary findings on route-specific abuse" below addresses the third bulleted statement by providing a review of the route of administration profile for original OxyContin® abuse.

NAVIPPRO™ patient assessment tools use the following operational definition of drug abuse: "use of an opioid analgesic in the past 30 days by an individual in substance abuse treatment that is not strictly in accordance with physician instructions." This operational definition of drug

Reference ID: 3292351

abuse seems to include both abuse[b] and misuse[c] according to the definitions presented at the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee (39). This operational definition of drug abuse also seems to capture medication errors[d].

Purdue argues that the NAVIPPRO™ operational definition of drug abuse is consistent with the Advisory Committee's definition of abuse for the following reasons:

- Treatment professionals consider any non-medical use of mind- or mood-altering substances among individuals with a substance use disorder as a 'relapse,' and therefore abuse.
- The patient assessment tools assess whether respondents used each drug for how the drug "made [the respondent] feel and not to help with pain", which indicates drug abuse behavior.
- The patient assessment tools aim to differentiate between legitimate use of pain medications and abuse by establishing that the respondents have a current pain problem, were prescribed an opioid medication for pain in the past 30 days, obtained pain medications only from his or her physician, and did not use the drug via a non-indicated route of administration.

For the above reasons, the Reviewer concurs with Purdue in that the NAVIPPRO™ definition of drug abuse is consistent with the definition of abuse[b] presented at the October 2010 Advisory Committee.

Overview of study methods/analyses

This overview of study methods details multiple interrelated analyses proposed or conducted by Purdue, or conducted by the Reviewer. In short, they are:

- analyses described in the **protocol**
- analyses conducted for the July 2012 **interim report**
- analyses conducted in **response** to FDA's **information requests**
- analyses conducted by the **Reviewer**

These analyses differ with respect to the following:

- study period definitions

---

[b] Abuse – as presented by the FDA at the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee, "the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effects it produces"

[c] Misuse – as presented by the FDA at the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee, "the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner"

[d] Medication error – according to the National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP), any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use (40)

Reference ID: 3292351

- routes of administration assessed
- the measures of drug abuse examined
- opioids assessed
- analytical approach

These analyses address the same broad objective, share the same basic study design, and use the same data source.

Objective

Broadly, the NAVIPPRO™ Investigation aims to characterize overall and route-specific abuse of reformulated OxyContin®. Specifically, the NAVIPPRO™ Investigation aims to

- compare the proportion of adults reporting past 30-day abuse of OxyContin® via any route of administration (including swallowing whole) before versus after marketing started for reformulated OxyContin®, among adults who reported prescription opioid abuse
- compare the proportion of those abusing OxyContin® by alternate routes of administration (snorting, injecting, or chewing) before versus after marketing started for reformulated OxyContin®, among individuals entering substance abuse treatment who reported abuse of OxyContin® in the past 30 days
- compare the change in the proportion of individuals who abuse OxyContin® via specific alternative routes of administration before versus after marketing started for reformulated OxyContin® to the corresponding change in the proportion of individuals who abuse comparator drugs by these routes across these same time periods
- compare the average number of days (out of the past 30 days) in which OxyContin® was abused before and after marketing started for reformulated OxyContin®, among individuals entering substance abuse treatment

To reduce confusion, the Reviewer has re-interpreted the statistic 'proportion' used in the first three bulleted objectives above. For the first objective, the Reviewer has interpreted the statistic "proportion" as a prevalence of opioid-specific abuse. For the second and third objective, the Reviewer has interpreted the statistic "proportion" as a percent of individuals who reported a specific route of administration if abusing a specific opioid.

The fourth objective refers to frequency of abuse, that is, number of days of abuse in the past 30 days. See "*Measures of drug abuse*" below.

Basic study design

The NAVIPPRO™ Investigation is a prevalence study with data collected prospectively from August 9, 2012, and retrospectively prior to August 9, 2012. See specific study dates below.

Study periods

In general, this investigation has two study periods with respect to when marketing started for reformulated OxyContin® (Table 3).

Reference ID: 3292351

The protocol states that the study period before marketing started would be from July 1, 2008, through July 31, 2010, and the study period after marketing started would be from January 1, 2011, through January 31, 2012. Accordingly, the transition period between the study periods would be from August 1, 2010, through December 31, 2010.

Because both formulations were available during the transition period, each formulation could be abused in that period. Abuse of original OxyContin® would be less expected after the transition period because substantially fewer prescriptions were dispensed for original OxyContin® after this period (see drug utilization data in Appendix C, Figure 40a).

However, the interim report did not account for a transition period. Instead, in the interim report, the study period before marketing started for reformulated OxyContin® was from July 1, 2009, through August 8, 2010, and the study period after marketing started was from August 9, 2010, through March 31, 2012. The interim report did not explain why the interim analyses' study period before marketing of reformulated OxyContin® was shorter than proposed in the protocol.

The interim report's study period definitions for the NAVIPPRO™ Investigation appropriately account for time reformulated OxyContin® is on the market, so the prevalence of reformulated OxyContin® abuse is not biased by the study period definitions. Still, NAVIPPRO™ analyses should carefully consider how the prevalence of abuse of extended-release (ER) oxycodone or original OxyContin® may affect prevalence of reformulated OxyContin® abuse, particularly during the *a priori* transition period.

Analyses conducted by Purdue in response to information requests from FDA also did not account for a transition period. Like the interim report's analyses, the study period before marketing started for reformulated OxyContin® was from July 1, 2009, through August 8, 2010. In addition, some of these analyses also used the interim report's definition for the study period after marketing started for reformulated OxyContin®. However, other analyses extended the study period after marketing started to September 30, 2012, because data through that time was available when these information request analyses were conducted.

The Reviewer conducted analyses for the same study periods defined in the July 2012 interim report because the data the Reviewer used for these analyses were aggregated for the two study periods defined in the interim report.

Table 3: Study periods for the NAVIPPRO™ Investigation, before and after marketing started for reformulated OxyContin®

Study period specified by	Study period before marketing started	Transition period	Study period after marketing started
Protocol	**Jul 1, 2008 – Jul 31, 2010**	**Aug 1, 2010 – Dec 31, 2010**	**Jan 1, 2011 – Jan 31, 2012**
Jul 2012 interim report	**Jul 1, 2009 – Aug 8, 2010**	**None**	**Aug 9, 2010 – Mar 31, 2012**
Responses to information requests	**Jul 1, 2009 – Aug 8, 2010**	**None**	**Aug 9, 2010 – Mar 31, 2012 or Aug 9, 2010 – Sep 30, 2012**
Reviewer	**Jul 1, 2009 – Aug 8, 2010**	**None**	**Aug 9, 2010 – Mar 31, 2012**

Reference ID: 3292351

Routes of administration

In general, the NAVIPPRO™ Investigation assesses overall (that is, not route-specific) abuse, oral abuse, and non-oral abuse (Table 4). This investigation also assesses more specific oral and non-oral routes of administration. Table 4 summarizes the routes of administration the protocol states that the NAVIPPRO™ Investigation aims to assess, and the routes of administration assessed in analyses conducted for interim report, for responses to information requests, and by the Reviewer.

Table 4: Proposed or conducted analyses examining routes of administration patterns of drug abuse

Route of administration	Protocol	Jul 2012 interim report	Responses to information requests	Reviewer's analyses
Any route	Yes	Yes	Yes	Yes
Any oral route	Yes	Yes	Yes	Yes
Swallow whole			Yes	
Chew and swallow	Yes		Yes	
Dissolve in mouth			Yes	
Drink in solution			Yes	
Any non-oral route	Yes	Yes	Yes	
Injection	Yes	Yes	Yes	Yes
Snorting	Yes	Yes	Yes	Yes
Smoking	Yes	Yes	Yes	Yes

Measures of drug abuse

This investigation examines various measures of drug abuse:

- prevalences of opioid-specific abuse
- prescription-adjusted rates of opioid-specific abuse
- prescription-adjusted prevalences of opioid-specific abuse,
- average frequency of abuse if abusing a specific opioid
- percent of individuals who report specific routes of administration if abusing a specific opioid

Reference ID: 3292351

Table 5: Proposed or conducted analyses examining various measures of drug abuse, including measures of overall (that is, not route-specific) and route-specific drug abuse

Measure of drug abuse	Overall or route-specific abuse assessed	Protocol	Jul 2012 interim report	Responses to information requests	Reviewer
Prevalence of opioid-specific abuse	Overall	Yes	Yes	Yes	
Prevalence of opioid-specific abuse	Route-specific	Yes		Yes	Yes
Prescription-adjusted rate of opioid-specific abuse	Overall	Yes			
Prescription-adjusted rate of opioid-specific abuse	Route-specific				
Prescription-adjusted prevalence of opioid specific abuse	Overall		Yes		
Average frequency of abuse	Overall	Yes	Yes		
Percent of individuals who report specific routes of administration if abusing a specific opioid	Route-specific	Yes	Yes	Yes	

Measures of drug abuse: Prevalences of opioid-specific abuse

Prevalence of opioid-specific abuse can be calculated for overall (that is, not route-specific) abuse, and for route-specific abuse. In addition, prevalence of opioid-specific abuse can be calculated for the population of all individuals assessed for substance abuse problems, and for the subset of those individuals who reported prescription opioid abuse. For example:

Equation 1

$$\text{prevalence of reformulated OxyContin® abuse} = \frac{\text{\# individuals who abused reformulated Oxycontin®}}{\text{\# individuals assessed}}$$

Equation 2

$$\text{prevalence of reformulated OxyContin® abuse} = \frac{\text{\# individuals who abused reformulated Oxycontin®}}{\text{\# individuals reporting prescription opioid abuse}}$$

As planned in the protocol, the interim report's analyses examined prevalence of opioid-specific <u>overall</u> abuse.

Responses to information requests analyzed the quarter-year prevalence of <u>overall</u> abuse of each OxyContin® formulation, as well as the route-specific prevalence of abuse of various categories of ER oxycodone per study period.

Supplementing these analyses, the Reviewer used data provided by Purdue to summarize the prevalence of route-specific ER oxymorphone and ER morphine abuse per study period. Purdue's data provided information on the number of adults abusing each opioid via specific routes of administration, and the number of individuals entering substance abuse treatment. Since the data was aggregated for the two study periods defined for the interim report, the Reviewer could not account for clustering of drug abuse patterns in clients who were admitted into substance abuse treatment multiple times. The Reviewer did not conduct any statistical tests assessing whether prevalence of route-specific abuse was significantly statistically different between opioids or between study periods.

Reference ID: 3292351

Measures of drug abuse: Prescription-adjusted rates

According to the protocol, this investigation plans to calculate prescription-adjusted rates of opioid-specific overall (that is, not route-specific) abuse. The protocol states that this rate of abuse will incorporate the number of prescriptions dispensed in U.S. retail pharmacies within the 3-digit zip codes where data is collected. As an example, the prescription-adjusted rate of abuse is calculated as:

Equation 3

$$\text{prescription-adjusted rate of reformulated OxyContin® abuse} = \frac{\text{\# individuals who abused reformulated Oxycontin®}}{\text{\# reformulated Oxycontin® prescriptions dispensed}}$$

The prescription data for the NAVIPPRO™ Investigation comes from Vector One National (VONA), a database of SDI Health LLC. VONA can project prescription information (such as, number of prescriptions dispensed) for the U.S., each U.S. state, and 3-digit zip codes.

Purdue used prescription data, according to ASI-MV® respondents' local 3-digit zip codes, to estimate prescription-adjusted rates of abuse. However, after using various overfitted models, the resulting estimates were unstable.

The Reviewer did not use data provided by Purdue to calculate prescription-adjusted rates of abuse because the catchment area for the abuse data (numerator of Equation 3) would not have been the same as the catchment area for the prescription data (denominator of Equation 3). Specifically, the catchment area for the drug abuse data was the ASI-MV® respondents' zip-codes. On the other hand, the catchment area for the prescription data was all states with ASI-MV® treatment centers. As a result, the catchment area for the denominator of Equation 3 was much larger than the catchment area for the numerator.

Hence, no prescription-adjusted rates of opioid-specific abuse are presented in this review.

Measures of drug abuse: Prescription-adjusted prevalences

In contrast to the protocol, the interim report presented prescription-adjusted prevalences of opioid-specific overall (that is, not route-specific) abuse. These prescription-adjusted prevalences of abuse incorporated projections of prescriptions dispensed in retail pharmacies located in states with ASI-MV® treatment centers. As an example, the prescription-adjusted prevalence of reformulated OxyContin® abuse is:

Equation 4

$$\text{prescription-adjusted prevalence of abuse} = \frac{\left(\dfrac{\text{\# individuals who abused reformulated Oxycontin®}}{\text{\# individuals assessed or \# individuals reporting prescription opioid abuse}}\right)}{\text{\# reformulated Oxycontin® prescriptions dispensed}}$$

The Reviewer noted that the prescription-adjusted prevalences calculated using Equation 4 are not easily interpretable. With simple algebraic manipulation, Equation 4 becomes:

Reference ID: 3292351

Equation 5

$$(\text{prescription - adjusted prevalence of abuse}) \times (\#\text{ reformulated Oxycontin® prescriptions dispensed}) = \frac{\#\text{ individuals who abused opioid}}{\#\text{ individuals assessed or }\#\text{ individuals reporting prescription opioid abuse}} = \text{prevalence of reformulated OxyContin® abuse}$$

Although Equation 5 is correct in implying that the prevalence of abuse is non-existent when the number of prescriptions dispensed is equal to zero, Equation 5 is incorrect in implying that the prevalence of abuse is greater than 100% when the number of prescription dispensed approaches infinity.

Moreover, the catchment area for the prevalence of abuse (numerator of Equation 4) was not the same as the catchment area for the prescription data (denominator of Equation 4). Specifically, the catchment area for the prevalence of abuse was the ASI-MV® respondents' zip-codes. On the other hand, the catchment area for prescription data was the all states with ASI-MV® treatment centers. As a result, the catchment area for the denominator of Equation 4 was much larger than the catchment area for the numerator.

Measures of abuse: Average frequency of abuse if abusing an opioid

The average frequency of opioid-specific overall (that is, not route-specific) abuse if abusing an opioid was defined as the average number of days of opioid-specific abuse in the past 30 days among individuals who reported abusing the opioid. This average is restricted to the range of 1 to 30 days. For example, the average frequency of reformulated OxyContin® abuse if abusing reformulated OxyContin® could range from 1 to 30 days. The interim report's analyses calculated the average frequency of opioid-specific abuse among those who reported abusing the opioid.

The NAVIPPRO™ data collection tools do not collect information on the frequency of route-specific abuse.

Measures of abuse: Percent of individuals who report specific routes of administration

Consistent with the protocol, the interim report also presented findings on the percent of individuals who, upon reporting abuse of an opioid, reported abusing the opioid via specific routes of administration. For example:

Equation 6

$$\%\text{ individuals reporting oral abuse of reformulated OxyContin®} = 100 \times \frac{\#\text{ individuals who orally abused reformulated OxyContin®}}{\#\text{ individuals who abused reformulated Oxycontin®}}$$

Opioids assessed

The interim report presented the prevalence and rate of opioid-specific abuse, average frequency of abuse if abusing an opioid, and the percent of individuals who report specific routes of administration, for the following opioids:

- the original OxyContin® formulation
- reformulated OxyContin®

Reference ID: 3292351

- OxyContin® regardless of formulation
- extended-release (ER) oxymorphone
- extended-release (ER) morphine

Analyses based on data submitted in response to information requests assessed prevalence of overall abuse for the following categories of ER oxycodone:

- any ER oxycodone
- all brand name U.S. ER oxycodone
- other ER oxycodone, that is, not brand name U.S. ER oxycodone
- U.S. original OxyContin®
- U.S. reformulated OxyContin®

Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified.

Other analyses of data submitted in response to information requests assessed the percent of individuals reporting specific routes of administration if abusing an opioid. The opioids assessed in these analyses were:

- the original OxyContin® formulation
- reformulated OxyContin®
- single-entity (SE) immediate-release (IR) oxycodone
- immediate-release (IR) hydrocodone combinations
- ER oxymorphone
- ER morphine

Statistical approach

According to a biostatistics review of this interim report, the statistical models used for this investigation are generally appropriate. The statistical analyses performed for this interim report were generalized estimating equations (GEE):

- Generalized linear mixed models
- Generalized log-binomial models

GEE accounted for clustering of observations among clients who were admitted into substance abuse treatment multiple times, as well as for nesting of respondents within a zip code. Generalized linear mixed models were used to estimate the changes in the prevalences of abuse and percent of individuals abusing each opioid via a specific route of administration. Generalized log-binomial models were used to estimate the frequency of abuse. For further details, see the biostatistics review (34).

Information request analyses used chi-square comparisons of percentages to test whether the prevalence of ER oxycodone abuse changed after marketing started for reformulated OxyContin®. This chi-square test did not account for potential clustering of observations among clients admitted multiple times into substance abuse treatment, or nesting of respondents within a zip code.

Reference ID: 3292351

Assumption required for interpreting preliminary findings

Selection bias may be operating in the NAVIPPRO™ Investigation if treatment centers contributing data earlier in the study period after marketing started for reformulated OxyContin® had different characteristics than treatment centers contributing data later on in that study period. It may be difficult to interpret the interim report's findings for the NAVIPPRO™ Investigation without assuming the following:

- The Reviewer assumes that the characteristics of substance abuse treatment centers (and their patients), which contributed data for the interim report's analyses, did not appreciably change throughout the investigation.

If this assumption were violated, then changes in the prevalence of reformulated OxyContin® abuse may simply reflect differences in treatment centers as they enter the investigation. Moreover, it follows that it may be inappropriate to compare the prevalence of reformulated OxyContin® abuse to original OxyContin® abuse throughout the study periods.

To understand how selection bias may be operating in this investigation, it is necessary to first understand that substance abuse treatment centers contributing data for the interim report's analyses varied throughout the investigation. These treatment centers selected for this investigation collected data on abuse of the two OxyContin® formulations before and after marketing started for reformulated OxyContin®. The investigation used this criterion for two reasons:

- Treatment centers may enter and leave the NAVIPPRO™ surveillance system.
- The substance abuse treatment centers did not uniformly update the ASI-MV® software, enabling respondents to identify reformulated OxyContin®.

Because of the non-uniformity of the software update, the treatment centers contributing data earlier in the study period after marketing started for reformulated OxyContin® may have updated their ASI-MV® software quicker than other treatment centers, and the reason for applying the update may have been related to a need to ascertain the formulation of OxyContin® being abused. Other factors may also explain the variations in the timing of the update.

In summary, the self-selection of treatment centers into the investigation is directly affected by ascertainment of reformulated OxyContin® and may be affected by a need to ascertain formulations of OxyContin® being abused, as might be the case if prevalence of OxyContin® abuse was high in these centers.

Figure 2 illustrates how the number and percent of substance abuse treatment centers collecting data on reformulated OxyContin® abuse increased from the third quarter of 2010 (3Q2010) to the first quarter of 2012 (1Q2012). The figure includes all sites, regardless of whether they were excluded from analyses. During the *a priori* transition period (3Q2010-4Q2010), the percent of treatment centers collecting data on reformulated OxyContin® was less than 70%. This percentage did not surpass (b) (4) until 2Q2011 and 4Q2011, respectively.

The percent of substance abuse treatment centers collecting data on reformulated OxyContin® abuse did not reach (b) (4) by 1Q2012. NAVIPPRO™ explained that some centers work remotely in geographic areas where little access to internet may hinder the ability to update software in a timely manner.

Reference ID: 3292351

Figure 2: Number and percent of treatment centers† that participated in the NAVIPPRO™ surveillance system and collected data on reformulated OxyContin® abuse

(b) (4)

Data Source: Purdue's response to FDA's Information Request, dated Nov 30, 2012.
†Purdue did not provide data on the number of treatment centers prior to 3Q2010.

Consequently, Figure 3 illustrates how the number of adults entering substance abuse treatment fluctuated throughout the investigation as a result of treatment centers entering and leaving the investigation.

Figure 3: Number of adults† entering substance abuse treatment, according to the NAVIPPRO™ surveillance system

(b) (4)

Data Source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 9" in the workbook NAVIPPRO System.xls.
†Clients admitted into substance abuse treatment more than once are counted multiple times.

The assumption that the characteristics of substance abuse treatment centers and their patients did not appreciably change throughout the investigation is testable. To test the assumption, this

Reference ID: 3292351

investigation could compare characteristics of the treatment centers entering the investigation versus those already in the investigation. In addition, this investigation could also compare characteristics of patients from treatment centers entering the investigation versus patients from treatment centers already in the investigation.

Characteristics of treatment centers to compare could include:

- the prevalence of original OxyContin® abuse before marketing started for reformulated OxyContin®, or in the quarter-year immediately prior to entering the investigation
- main funding source (public or private)
- geographic location

Characteristics of patients to compare could include:

- demographics, such as age and sex
- clinical characteristics, such as addiction severity
- substance use characteristics, such as injection use history

Purdue did not provide information on the characteristics of the treatment centers already in versus entering the investigation, or characteristics of patients attending these respective treatment centers.

Preliminary findings on overall abuse

From June 1, 2009, through August 8, 2010, the NAVIPPRO™ Investigation included (b) (4) adults who entered substance abuse treatment, of whom (b) (4) adults reported abusing prescription opioids. From August 9, 2010, through March 31, 2012, the NAVIPPRO™ Investigation included (b) (4) adults who entered substance abuse treatment, of whom (b) (4) adults reported abusing prescription opioids. Note: Adults admitted into substance abuse treatment more than once are double-counted.

The number of adults reporting original OxyContin® abuse was (b) (4) before marketing started for reformulated OxyContin®, and (b) (4) adults reported reformulated OxyContin® abuse afterward.

Table 6 summarizes the sample characteristics of the adults who reported prescription opioid abuse.

Reference ID: 3292351

Table 6: NAVIPPRO™ Investigation sample characteristics for adults who reported prescription opioid abuse from June 1, 2009, through March 31, 2012

(b) (4)

Data Source: Section 4.1.4.1 of the interim report entitled "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"

† Includes some clients who were admitted into substance abuse treatment more than once

The interim report did not provide any additional information on the characteristics of the total sample assessed for the NAVIPPRO™ Investigation. Alongside the demographic information above, pertinent characteristics to describe the sample include: admittance into a publicly versus privately funded treatment center and geographic location.

Prevalence of abuse of any ER oxycodone product fell after marketing started for reformulated OxyContin® (Figure 4, Table 7, Figure 5, and Table 8). This was true for all adults entering substance abuse treatment, and among the subset of adults reporting prescription opioid abuse.

Specifically, among all adults entering substance abuse treatment, the prevalence of ER oxycodone abuse after marketing started for reformulated OxyContin® (b) (4) was (b) (4) lower than before marketing started (b) (4) (Figure 4 and Table 7). Similarly, among the subset of adults who reported prescription opioid abuse, the prevalence of ER oxycodone abuse after marketing started (b) (4) was (b) (4) lower than before marketing started (b) (4) (Figure 5 and Table 8).

Reference ID: 3292351

Figure 4: Prevalence of abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Table 7: Prevalence of abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Reformulated OxyContin® was not marketed before Aug 9, 2010.

Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified

Reference ID: 3292351

Figure 5: Prevalence of abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Table 8: Prevalence of abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Reformulated OxyContin® was not marketed before Aug 9, 2010.

Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified

Reductions in abuse of other ER oxycodone (that is, not brand name U.S. ER oxycodone) drove the reductions in any ER oxycodone abuse (Figure 6 and Figure 7). This was true for all adults entering substance abuse treatment, and among the subset of adults reporting prescription opioid abuse. These reductions were consistent with the reductions in prescriptions dispensed for

Reference ID: 3292351

generic ER oxycodone after marketing started for reformulated OxyContin® (see drug utilization data in Appendix C, Figure 40a). Note: The category 'other ER oxycodone' includes generic ER oxycodone, OxyContin® from Canada and Mexico, and ER oxycodone whose formulation and country of origin was unknown. Thus, the reductions in 'other ER oxycodone' could be influenced by availability and abuse of formulations other than generic ER oxycodone.

Figure 6: Stacked bar graph of the prevalence of abuse of either brand name U.S. ER oxycodone (OxyContin®) or other ER oxycodone, or both of these, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Figure 7: Stacked bar graph of the prevalence of abuse of either brand name U.S. ER oxycodone (OxyContin®) or other ER oxycodone, or both of these, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Reference ID: 3292351

Information request analyses found that the prevalence of abuse of OxyContin® regardless of formulation statistically significantly declined, but the reduction was rather small (Figure 4, Table 7, Figure 5, and Table 8). Specifically, among all adults entering substance abuse treatment, the prevalence of abuse of OxyContin® regardless of formulation fell from (b) (4) before marketing started to (b) (4) after marketing started, a relative percent difference of only (b) (4). Among adults who reported prescription opioid abuse, this relative percent difference was larger.

Several preliminary findings suggest that overall abuse (that is, not route-specific abuse) of reformulated OxyContin® was statistically significantly lower than abuse of the original OxyContin® formulation (Figure 8, Table 9, Figure 9, and Table 10). These findings were true for all adults entering substance abuse treatment and for the subset of adults reporting prescription opioid abuse.

Specifically, among all adults entering substance abuse treatment, the prevalence of overall abuse of reformulated OxyContin® (b) (4) was (b) (4) lower than the prevalence of overall abuse of original OxyContin® before marketing started for reformulated OxyContin® (b) (4), a statistically significant finding (Figure 8 and Table 9). Among the subset of adults reporting prescription opioid abuse, this difference in prevalences was larger (Figure 9 and Table 10).

Figure 8: Prevalence of abuse of specific opioids among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data Source: Table 9 of the interim report entitled "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"

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the prevalences shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Prevalence of OxyContin® abuse during Aug 9, 2010, to Mar 31, 2012, was calculated for only reformulated OxyContin®.

Reference ID: 3292351

Table 9: Prevalence of abuse of specific opioids among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data Source: Table 9 of the interim report entitled "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"

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the prevalences shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once. Reported in this table is the number of unique clients.

‡Prevalence of OxyContin® abuse during Aug 9, 2010, to Mar 31, 2012, was calculated for only reformulated OxyContin®

Figure 9: Prevalence of abuse of specific opioids among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data Source: Table 9 of the interim report entitled "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"

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the prevalences shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Prevalence of OxyContin® abuse during Aug 9, 2010, to Mar 31, 2012, was calculated for only reformulated OxyContin®.

Reference ID: 3292351

Table 10: Prevalence of abuse of specific opioids among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data Source: Table 9 of the interim report entitled "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"

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the prevalences shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once. Reported in this table is the number of unique clients.

‡Prevalence of OxyContin® abuse during Aug 9, 2010, to Mar 31, 2012, was calculated for only reformulated OxyContin®.

Conversely, compared to the study period before marketing of reformulated OxyContin®, reductions in the prevalence of overall abuse were absent or small for the opioid comparators ER oxymorphone and ER morphine (Figure 8, Table 9, Figure 9, and Table 10). After marketing started for reformulated OxyContin®, prevalence of ER oxymorphone abuse statistically significantly increased by (b) (4) for all adults entering substance abuse treatment, and by (b) (4) for the subset of adults reporting prescription opioid abuse. For all adults entering substance abuse treatment and for the subset of adults reporting prescription opioid abuse, prevalence of ER morphine abuse was similar before and after marketing started for reformulated OxyContin®.

In a response to an information request, Purdue provided data on the quarter-year prevalence of overall abuse for each opioid. Figure 10 illustrates trends in the prevalence of abuse of OxyContin® (regardless of formulation as well as for each formulation), ER oxymorphone, and ER morphine.

The prevalence of original OxyContin® abuse:

- increased from (b) (4) in the third quarter of 2009 (3Q2009) to (b) (4) in the third quarter of 2010 (3Q2010)
- decreased from (b) (4) in 3Q2010 to (b) (4) in 2Q2011
- seemed to be steady at about (b) (4) from 2Q2011 onward

The prevalence of reformulated OxyContin® abuse seemed to be steady at about (b) (4) from 3Q2010 to the 1Q2012.

Meanwhile, the prevalence of abuse of OxyContin® regardless of formulation;

- decreased from (b) (4) in 3Q2010 to (b) (4) in 2Q2011

Reference ID: 3292351

- seemed steady at about (b) (4) from 2Q2011 onward

From 3Q2009 to 1Q2012, the prevalence of ER oxymorphone abuse increased from (b) (4) to (b) (4), and the prevalence of ER morphine abuse seemed to be steady at (b) (4).

Figure 10: Prevalence of abuse of specific opioids‡ among adults† who entered substance abuse treatment, from the third quarter of 2009 (3Q2009) to the first quarter of 2012 (1Q2012)

(b) (4)

Data Source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 9" in the workbook NAVIPPRO System.xls.

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the prevalences shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Marketing started for reformulated OxyContin® in Aug 9, 2010, which is in 3Q2010.

Using generalized estimating equations, Purdue found that the prevalence of abuse of OxyContin® regardless of formulation was not statistically significantly different between the study periods before and after marketing started for reformulated OxyContin®. Note: Table 7 shows a statistically significant decrease in the prevalence of abuse of OxyContin® regardless of formulation, but Table 7 does not use generalized estimating equations to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once. This lack of statistical significance was likely affected by:

- the availability of both original and reformulated OxyContin® from August 9, 2010, to December 31, 2010 (an *a priori* transition period)
- the persistence of original OxyContin® abuse from April 2011 onward

When Purdue excluded data from the *a priori* transition period, the prevalence of abuse of OxyContin® regardless of formulation was (b) (4) lower after marketing started for reformulated OxyContin, a statistically significant finding.

The interim report presented prescription-adjusted prevalences of abuse for original and reformulated OxyContin®, ER oxymorphone, and ER morphine, but, as discussed previously, the prescription-adjusted prevalences were not easily interpretable. Also, the Reviewer could not appropriately calculate the prescription-adjusted rates of abuse given the limitations of the data sources.

Reference ID: 3292351

It appears that adults who abused reformulated OxyContin® do so less frequently than adults who abused the original OxyContin® formulation (Figure 11 and Table 11). Specifically, among adults who abused original OxyContin® before marketing started for reformulated OxyContin®, the average frequency of original OxyContin® abuse was 10.6 days in the past 30 days. In comparison, the average frequency of reformulated OxyContin® abuse was statistically significantly lower (7.5 days). Meanwhile, the frequency of ER oxymorphone abuse among adults reporting ER oxymorphone abuse statistically significantly increased after marketing started for reformulated OxyContin®. On the other hand, the frequency of ER morphine abuse among adults reporting ER morphine abuse did not statistically significantly change.

Figure 11: Frequency of abuse of specific opioids in the past 30-days prior to intake, among adults[†] entering substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after[‡] (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data Source: Table 11 of the interim report entitled "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"

[†]Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the frequencies shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

[‡]Average frequency of OxyContin® abuse during Aug 9, 2010, to Mar 31, 2012, was calculated for only reformulated OxyContin®.

Reference ID: 3292351

Table 11: Frequency of opioid-specific abuse in the past 30-days prior to intake, among adults[†] entering substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after[‡] (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

[redacted]

Data Source: Table 11 of the interim report entitled "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"

[†]Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the frequencies shown here with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

[‡]Average frequency of OxyContin® abuse during Aug 9, 2010, to Mar 31, 2012, was calculated for only reformulated OxyContin®.

Division of Epidemiology II Reviewer comments on the preliminary findings on overall abuse

Although the above findings suggest a lower overall abuse of reformulated OxyContin® compared to the original OxyContin® formulation, the above findings are also mixed because of the following:

- Original OxyContin® abuse persisted after marketing started for reformulated OxyContin® (Figure 10).
- The prevalence of overall abuse of OxyContin® regardless of reformulation was similar between the timeframe of 2Q2011 to 1Q2012 and the quarter-year of 3Q2009 (Figure 10).

Note: The Reviewer could not comment on the possible persistence of other ER oxycodone[e] abuse because the Reviewer did not have information on abuse of other ER oxycodone through time, similar to the information shown in Figure 10.

The persistence of overall abuse of original OxyContin® from 2Q2011 onward is unexpected (Figure 10). According to drug utilization data, prescriptions dispensed for original OxyContin® precipitously dropped after the manufacturer stopped shipments of original OxyContin® on August 5, 2010 (see drug utilization data in Figure 40a of Appendix C). Therefore, the Reviewer expected that the trend in the prevalence of original OxyContin® abuse would continue to decrease from 2Q2011 to 1Q2012. Some possible explanations for this finding include:

- Misclassification of reformulated OxyContin® abuse as original OxyContin® abuse may exist.

---

[e]In this context, other ER oxycodone refers to generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified.

Reference ID: 3292351

- A time lag between dispensing and abusing original OxyContin® could be long.
- Availability of counterfeit original OxyContin®, or diversion of original OxyContin®, from markets outside of the U.S. could have sustained levels of original OxyContin® abuse.

However, these explanations are speculative for the following reasons:

- The validity of exposure classification with the ASI-MV® is unknown.
- The time lag from opioid dispensing to opioid abuse is unknown.
- The availability of diverted or counterfeit original OxyContin® is not truly known.

The stagnant prevalence of overall abuse of OxyContin® regardless of reformulation was similar between the timeframe of 2Q2011 to 1Q2012 (prevalence of (b) (4)), when reformulated OxyContin® was marketed, and 3Q2009 (3.2%), when only original OxyContin® was marketed (Figure 10). This finding is likely affected by the persistence of original OxyContin® abuse from 2Q2011 to 1Q2012.

The pre-post comparison of the prevalence of original OxyContin® abuse before marketing of reformulated OxyContin® to the prevalence of reformulated OxyContin® abuse inherently assumes that original OxyContin® would not be abused appreciably, especially after a reasonable transition period. However, persisting prevalence of original OxyContin® abuse was observed, so confounding by the persistence of original OxyContin® abuse makes it difficult to assess how prevalent reformulated OxyContin® abuse may be when original OxyContin® is not being abused. Abuse of original OxyContin® (confounder) is associated with the study period (the 'intervention,' since study period delineates 'exposure' to reformulated OxyContin®), and is likely inversely associated with reformulated OxyContin® abuse. Because of the persistence in original OxyContin® abuse, it is still unknown whether individuals abusing original OxyContin® will switch to reformulated OxyContin® when the licit and illicit supply of original OxyContin® is depleted.

Assessing changes in the prevalence of abuse of OxyContin® regardless of formulation removes the confounding described above. However, misclassification of abuse of other ER oxycodone (such as generic ER oxycodone) as OxyContin® is possible and may partially explain the decreases in the prevalence of OxyContin® abuse after marketing started for reformulated OxyContin®. Because reported abuse of other ER oxycodone products decreased, misclassification could have contributed to the observed decreases in the prevalence of OxyContin® abuse. Whether potential misclassification between generic ER oxycodone and OxyContin® is differential or non-differential is not known.

Lastly, assessing changes in the prevalence of ER oxycodone abuse removes the confounding described above as well as the misclassification between ER oxycodone formulations. However, the declines in the prevalence of ER oxycodone abuse were driven by reductions in abuse of other ER oxycodone (such as generic ER oxycodone), not OxyContin® (Figure 4, Table 7, Figure 5, Table 8, Figure 6, and Figure 7). Furthermore, these declines in ER oxycodone abuse could reflect the declines in ER oxycodone prescriptions dispensed; no analysis in this investigation appropriately incorporated a measure of the availability of ER oxycodone.

The prevalence of original OxyContin® abuse during the study period before marketing started for reformulated OxyContin® underestimates the prevalence of abuse of the original formulation of ER oxycodone during that period (Table 7 and Table 8). However, the prescription-adjusted rate of ER oxycodone abuse may or may not be the same as the prescription-adjusted rate of original OxyContin® abuse. That is, although the number of adults abusing any ER oxycodone product is higher than the number of adults abusing original OxyContin®, the number of

Reference ID: 3292351

prescriptions dispensed for any ER oxycodone would also be higher than the number of prescriptions dispensed for original OxyContin®. The interim report did not present prescription-adjusted rates of abuse.

Comparing ER oxycodone abuse, original OxyContin® abuse, and reformulated OxyContin® abuse is very difficult without analyses that incorporate data on prescriptions dispensed for these opioids. In particular, the prescription volume for each of these categories of ER oxycodone varied widely during the study periods (Figure 40a).

The Reviewer noted that the persistence of original OxyContin® abuse also confounds the findings on how frequently each OxyContin® formulation was abused. Specifically, the persisting abuse of original OxyContin® may result in a lower frequency of reformulated OxyContin® abuse among those who abused OxyContin®, in general. For example, under the assumption that the two Oxycontin® formulations are equally substitutable for abuse, a client who reports 30 days of abuse of OxyContin® regardless of formulation in the past 30-days could have reported some days abusing original OxyContin®, other days abusing reformulated OxyContin®, and the rest of the days abusing both formulations. Thus, the days of abuse of reformulated OxyContin® would be ≤ 30 days in the presence of original OxyContin® abuse, and would be equal to 30 days in the absence of original OxyContin® abuse.

The Reviewer also noted that the prevalence of overall abuse of reformulated OxyContin® was still higher than the prevalence of overall abuse of the opioid comparators (Figure 9 and Table 10). However, comparing prescription-adjusted rates of overall abuse among the opioids is more appropriate than only comparing prevalences of abuse, but comparing prescription-adjusted rates among the opioids was not possible with the current data. Furthermore, Purdue did not use any formal statistical analysis to compare the prevalence of abuse between opioids, and this type of comparison is not an objective of this investigation.

This investigation's ability to assess OxyContin® abuse among an at-risk population (that is, individuals entering substance abuse treatment) is both a strength and a limitation of this investigation. Specifically, unlike a general population, an at-risk population will have better statistical power to observe reductions in OxyContin® abuse. By only assessing individuals at high risk of OxyContin® abuse, the prevalence rates of OxyContin® abuse would be higher relative to prevalence rates among the general population, so the differences in abuse rates between formulations, if they exist, could be detected more easily.

However, the NAVIPPRO™ study population only includes individuals who survived drug abuse prior to entering substance abuse treatment. It is possible that, among individuals entering substance abuse treatment, a decrease in the number of individuals reporting OxyContin® abuse could reflect an increasing number of deaths that preclude entering into treatment. Other studies – particularly the NPDS Investigation and the RADARS® SPCP Investigation – in Purdue's postmarketing study program could provide insight into changes in mortality associated with OxyContin®.

In order to generalize the results of NAVIPPRO™ Investigation to the general population, three questions must be asked:

1. Are the abuse patterns found in this interim report similar to abuse patterns observed among all treatment centers participating in the NAVIPPRO™ surveillance system?
2. If so, are the treatment centers participating in the NAVIPPRO™ surveillance system similar to all treatment centers in the U.S.?
3. If so, do (routes of) abuse patterns of individuals entering treatment centers in the U.S. reflect abuse patterns of individuals not entering treatment?

Reference ID: 3292351

As was stated in above in "Assumption required for interpreting preliminary findings," Purdue has not provided information on characteristics of treatment centers contributing versus not contributing data to these analyses. Purdue provided demographic information for the second question suggesting that, indeed, the treatment centers participating in the NAVIPPRO™ surveillance system are similar to other treatment centers, particularly those that contribute data to the Treatment Episode Data Set (TEDS). Lastly, the third question requires information outside the scope of this investigation, but could be enlightened by national survey data.

Preliminary findings on route-specific abuse

The NAVIPPRO™ Investigation is the only formal study to have preliminary findings on route-specific abuse.

Preliminary findings found that prevalence of reformulated OxyContin® via oral and non-oral routes was statistically significantly lower than prevalence of abuse of original OxyContin® via these same routes (Figure 12a, Figure 12b, Table 12, Figure 13a, Figure 13b, and Table 13). These findings were true for all adults entering substance abuse treatment and for the subset of adults reporting prescription opioid abuse.

Specifically, among all adults entering substance abuse treatment, the prevalence of oral abuse of reformulated OxyContin® was (b) (4) lower than the prevalence of oral abuse of original OxyContin® before marketing started for reformulated OxyContin®. Additionally, the prevalence of non-oral abuse of reformulated OxyContin® was (b) (4) lower than the prevalence of non-oral abuse of original OxyContin® before marketing started for reformulated OxyContin®. Among the subgroup of adults reporting prescription opioid abuse, these relative percent differences were slightly larger.

Reference ID: 3292351

Figure 12a: Prevalence of <u>oral abuse</u> of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Note: The comparison performed in the interim report was between the prevalence of original OxyContin® before marketing started for reformulated OxyContin® versus prevalence of abuse of reformulated OxyContin®.

Figure 12b: Prevalence of <u>non-oral abuse</u> of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Note: The comparison performed in the interim report was between the prevalence of original OxyContin® before marketing started for reformulated OxyContin® versus prevalence of abuse of reformulated OxyContin®.

Reference ID: 3292351

Table 12: Prevalence of abuse of various categories of OxyContin® extended-release (ER) oxycodone abuse, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by route of administration

(b) (4)

[redacted]

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Reformulated OxyContin® was not marketed before Aug 9, 2010.

^Prevalence of reformulated OxyContin® abuse via oral and non-oral routes was statistically significantly lower by (b) (4) and (b) (4), respectively, relative to the prevalence of original OxyContin® abuse before marketing started for reformulated OxyContin®.

Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified

*Statistically significant at p-value < 0.05

Reference ID: 3292351

Figure 13a: Prevalence of <u>oral abuse</u> of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Note: The comparison performed in the interim report was between the prevalence of original OxyContin® before marketing started for reformulated OxyContin® versus prevalence of abuse of reformulated OxyContin®.

Figure 13b: Prevalence of <u>non-oral abuse</u> of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Note: The comparison performed in the interim report was between the prevalence of original OxyContin® before marketing started for reformulated OxyContin® versus prevalence of abuse of reformulated OxyContin®.

Reference ID: 3292351

Table 13: Prevalence of abuse of various categories of OxyContin® extended-release (ER) oxycodone abuse, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by route of administration

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Reformulated OxyContin® was not marketed before Aug 9, 2010.

^Prevalence of reformulated OxyContin® abuse via oral and non-oral routes was statistically significantly lower by (b) (4) and (b) (4) respectively, relative to the prevalence of original OxyContin® abuse before marketing started for reformulated OxyContin®.

Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified

*Statistically significant at p-value < 0.05

In a response to an FDA information request, Purdue noted that the route of administration profile for ER oxycodone abuse remained relatively unchanged after marketing started for reformulated OxyContin® (Figure 14a-e and Table 14a-e).

Purdue also noted that reformulated OxyContin® was less likely to be abused through non-oral routes of administration than the other ER oxycodone categories assessed (Figure 14a-e and Table 14a-e). Indeed, abuse of reformulated OxyContin® was more oral, and less non-oral, than abuse of original OxyContin®. Among those who abused **original** OxyContin®, approximately **55%** reported abusing original OxyContin® via **oral** routes, and approximately **70%** reported abuse via **non-oral** routes. Meanwhile, among those who abused **reformulated** OxyContin®, approximately **75%** reported abusing reformulated OxyContin® via **oral** routes, and approximately **40%** reported abuse via **non-oral** routes. This lower percentage of reformulated

Reference ID: 3292351

OxyContin® abuse via every non-oral routes of administration contributed to a higher percentage of reformulated OxyContin® abuse via oral routes of administration.

In Figure 14a-e and Table 14a-e, the sum of the percent of all the routes of administration per opioid is greater than 100% because adults may report abuse of each opioid via several routes of administration.

Figure 14a: Percent of adults[†] who, upon stating that they abused extended-release (ER) oxycodone, reported oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Reference ID: 3292351

Figure 14b: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported non-oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Figure 14c: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported injecting ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Figure 14d: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported smoking ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Figure 14e: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported snorting ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The figures do not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Reference ID: 3292351

Table 14a: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Table 14b: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported non-oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Reference ID: 3292351

Table 14c: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported injecting ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Table 14d: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported smoking ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Reference ID: 3292351

Table 14e: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported snorting ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data in the tables do not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Exploratory analyses for the interim report found that original OxyContin® abuse via specific non-oral routes of administration did not change substantially after marketing started for reformulated OxyContin® (Figure 14b-e and Table 14b-e). For example, among adults who reported original OxyContin® abuse, a similar percentage reported injecting and snorting of original OxyContin® before and after marketing started for reformulated OxyContin®.

However, data obtained in response to a subsequent information request suggested that the route of administration profile for original OxyContin® abuse may have started shifting in 2Q2012 away from non-oral abuse (Figure 15b) towards a more oral pattern of abuse, that is, more similar to the routes of administration profile for reformulated OxyContin® abuse (Figure 15a). The shift away from non-oral abuse was more noticeable for injection (Figure 15c) than for snorting (Figure 15d). The percent of adults who reported OxyContin® abuse via smoking did not appreciably change after marketing started for reformulated OxyContin®

These changes in the routes of administration patterns observed for original OxyContin® are subtle, so the routes of administration patterns are still distinct between the two formulations (Figure 15a-c, see also Figure 41a and Figure 41b in Appendix D).

Meanwhile, routes of abuse patterns for reformulated OxyContin® seemed stable, with oral routes of reformulated OxyContin® abuse being more prevalent than non-oral routes of abuse (Figure 41b).

Reference ID: 3292351

Figure 15a: Percent of adults[α] who reported <u>oral</u> routes of administration, among those who abused original or reformulated OxyContin®, from the third quarter of 2009 (3Q2009) to the first quarter of 2012 (1Q2012)

(b) (4)

Figure 15b: Percent of adults[α] who reported <u>non-oral</u> routes of administration, among those who abused original or reformulated OxyContin®, from the third quarter of 2009 (3Q2009) to the first quarter of 2012 (1Q2012)

(b) (4)

Reference ID: 3292351

Figure 15c: Percent of adults[α] who reported injection, among those who abused original or reformulated OxyContin®, from the third quarter of 2009 (3Q2009) to the first quarter of 2012 (1Q2012)

(b) (4)

Figure 15d: Percent of adults[α] who reported snorting, among those who abused original or reformulated OxyContin®, before (3Q2009-2Q2010) and after (3Q2010-3Q2012) marketing started for reformulated OxyContin®

(b) (4)

Reference ID: 3292351

Figure 15e: Percent of adults[α] who reported smoking, among those who abused original or reformulated OxyContin®, before (3Q2009-2Q2010) and after (3Q2010-3Q2012) marketing started for reformulated OxyContin®

(b) (4)

[†]The figures include data from Jun 1, 2009, which is in 3Q2009, through Sep 30, 2012, which is in 3Q2012.

[‡]Marketing started for reformulated OxyContin® on Aug 9, 2010, which is in 3Q2010.

[α]Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

When calculating the prevalence of abuse for the opioid comparators, the Reviewer found that the prevalence of oral and non-oral abuse of ER oxymorphone increased (Figure 16 and Figure 17). Meanwhile, the prevalence of oral and non-oral abuse of ER morphine did not appreciably change.

Reference ID: 3292351

Figure 16: Prevalence of route-specific abuse of specific opioids among adults† entering substance abuse treatment before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Table 9," Figure 11," "Figure 12," and "Figure 13" in the workbook NAVIPPRO System.xls.

†Clients admitted into substance abuse treatment more than once are counted multiple times. Prevalences shown here do not account for clustering of drug abuse patterns among clients admitted into substance abuse treatment more than once.

Figure 17: Prevalence of route-specific abuse of specific opioids among adults† who entered substance abuse treatment and reported abuse of prescription opioids, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Table 9," Figure 11," "Figure 12," and "Figure 13" in the workbook NAVIPPRO System.xls.

†Clients admitted into substance abuse treatment more than once are counted multiple times. Prevalences shown above do not account for clustering of drug abuse patterns among clients admitted into substance abuse treatment more than once.

Reference ID: 3292351

Among those who abused the comparator opioids – ER oxymorphone and ER morphine – abuse via non-oral routes of administration did not decrease after marketing started for reformulated OxyContin® (Figure 18 and Table 15). Specifically, the percent of adults who reported snorting ER oxymorphone if abusing ER oxymorphone statistically significantly increased from (b) (4) before to (b) (4) after marketing started for reformulated OxyContin®. Similarly, the percent of adults who reported injecting ER oxymorphone if abusing ER oxymorphone statistically significantly increased from (b) (4) Non-oral abuse of ER morphine did not significantly change after marketing started for reformulated OxyContin®.

Figure 18: Percent of adults who, upon reporting that they abused extended-release (ER) oxymorphone or ER morphine, reported specific routes of administration for abuse of those opioids, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specific the worksheets "Figure 11", "Figure 12", and "Figure 13" in the workbook NAVIPPRO System.xls

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the percentages shown above with GEE modeling to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Reference ID: 3292351

Table 15: Percent of adults† who, upon stating that they abused specific opioids, reported specific routes for abuse of the opioids, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

[redacted]

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 11", "Figure 12", and "Figure 13" in the workbook NAVIPPRO System.xls.

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the percentages shown above with GEE modeling in order to account for clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

*Statistically significant difference (p-value < 0.0001), relative to percent reporting the respective route of administration before marketing started for reformulated OxyContin®

As stated above, the Reviewer could not calculate the prescription-adjusted rates of route-specific abuse per opioid.

Information request analyses summarized abuse via specific oral routes of administration – swallowing whole, chewing and then swallowing, dissolving in mouth, and drinking in a solution – for the period from January 1, 2012, to March 31, 2012 (Figure 19). However, Purdue did not provide data on abuse via specific oral routes of administration for the study period before marketing started for reformulated OxyContin®. Therefore, changes in abuse patterns for specific oral routes of administration cannot be determined.

Reference ID: 3292351

Figure 19: Percent of adults† who, upon stating that they abused specific opioids, reported specific oral routes of administration for abuse of the opioids, after (January 1, 2012, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Tables 1 and 2 of Purdue's response to FDA's Information Request, dated Nov 30, 2012

Division of Epidemiology II Reviewer comments on the preliminary findings on route-specific abuse

The above findings suggest that abuse of reformulated OxyContin® was lower than abuse of original OxyContin® via non-oral routes of administration.

However, these above findings are not based on complete evaluations for the following reasons:

- The prevalent abuse of original OxyContin® and, possibly other ER oxycodone, precludes a complete assessment of the route of administration profile for reformulated OxyContin® abuse (Figure 4, Table 7, Figure 5, Table 8, and Table 12).
- Prescription-adjusted rates of route-specific abuse per opioid were not presented.
- More information on specific oral routes of administration is needed for the period before reformulated OxyContin® was first marketed.

A complete assessment of the route of administration profile for reformulated OxyContin® abuse cannot be performed at this time because abuse of original OxyContin® persisted after marketing of reformulated OxyContin®. That is, it cannot be determined at this time whether clients of substance abuse treatment will abuse reformulated OxyContin® more via non-oral routes of administration after they have exhausted all licit and illicit supplies of original OxyContin®. Still, the current findings on the route of administration profile for reformulated OxyContin® abuse when both formulations are being abused suggest that its profile is much less non-oral and more oral (Figure 15a-e, Figure 41a, and Figure 41b).

Future analyses of NAVIPPRO™ data will need to appropriately adjust routes of abuse findings with a measure of the availability of OxyContin®. Doing so will help assess whether reductions in the prevalence of route-specific OxyContin® abuse simply reflect a lower number of OxyContin® prescriptions dispensed after marketing started for reformulated OxyContin® (Figure 40a).

More information on specific oral routes of administration is needed for the period before marketing started for reformulated OxyContin®. Purdue's study program should examine whether there was a shift in non-oral routes of original OxyContin® abuse to oral routes of reformulated OxyContin® abuse that require tampering with the reformulation (such as chewing). This examination would determine whether specific oral routes of administration, such as drinking and chewing, may have changed after marketing started for reformulated OxyContin®.

Reference ID: 3292351

Although differential misclassification of abuse of reformulated OxyContin® as abuse of original OxyContin® may be present in the NAVIPPRO™ Investigation, abuse of original OxyContin® does seem to truly persist long after distribution of original OxyContin® to pharmacies ceased. Figure 15a-e suggests that the routes of abuse patterns for original OxyContin® seemed to be shifting away from non-oral routes of administration to oral routes of administration, as would be expected if abuse of reformulated OxyContin® were misclassified as abuse of original OxyContin®. However, Figure 15a-e, Figure 41a, and Figure 41b also suggested that each OxyContin® formulation had a different route of abuse profile through 3Q2012. Therefore, in the Reviewer's opinion, while misclassification may be present, abuse of original OxyContin® was also continuing through 3Q2012.

Division of Epidemiology II's requested clarifications and modifications

Assessment of the severity or duration of addiction to OxyContin® specifically, or to opioids in general, would greatly enhance the understanding of the association between the introduction of reformulated OxyContin® to the market and the clinical outcome of addiction. However, it is unknown if the NAVIPPRO™ data collection tool (ASI-MV®) can assess severity or duration of addiction. The Reviewer recommends that Purdue clarify whether NAVIPPRO™ incorporates an assessment of severity or duration of addiction.

Reference ID: 3292351

3.1.2 Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP)

Data source/data collection

RADARS® is a surveillance system that collects prescription drug abuse, misuse, and diversion data throughout the U.S. RADARS® SPCP specifically collects data on calls to poison centers for exposures to substances, including opioids. (b) (4) out of the total of (b) (4)[f] regional poison centers provide data to RADARS® SPCP on exposure calls, and these (b) (4) poison centers cover (b) (4) states, including over (b) (4) people in urban, suburban, and rural regions. No poison centers have left RADARS® since joining the RADARS® System, and from the fourth quarter of 2008 through the first quarter of 2012, centers enrolling into RADARS® have slightly increased its U.S. population coverage from approximately (b) (4) to approximately (b) (4)

In July 2010 (prior to the introduction of reformulated OxyContin®), a reformulated OxyContin® product code was added to the Poisindex drug index, the exposure database used by all U.S. regional poison centers. Although this product code is readily available to poison centers that use the online version of Poisindex, most poison centers update their software via CD-ROM every 3 to 6 months, so ascertainment of reformulated OxyContin® exposures may be hindered until the software update. In addition, Table 37 in Appendix F suggests that poison centers did not differentiate reformulated OxyContin® from original OxyContin® until the fourth quarter of 2010. Lastly, the Poisindex specifically marked the original formulations of OxyContin® as 'discontinued,' although this code could still be used to classify exposures.

For each exposure case, Specialists in Poison Information ask callers detailed questions to identify the exposure as accurately as possible, including ascertaining an exposure from a drug product's label, shape, color, and imprint. The Specialists in Poison Information also use a nationally standardized data collection tool to code reasons for exposure reported by callers to poison centers (41). Examples of reasons for exposure include "intentional abuse exposure" and "unintentional general exposure" (see Appendix E for full list).

Using the standard data collection methodology of all U.S. poison centers, RADARS® SPCP collects exposure data for various formulations of oxycodone (see Appendix F for the various formulations). In addition, RADARS® performs a systematic case review to validate and ensure the accuracy of reported drug exposure data. For example, while the standard practice among poison centers is to only record a product verbatim as reported by a caller, RADARS® has used case notes to recode exposures (such as 'ER oxycodone' to 'OxyContin®' or vice-versa) in (b) (4) of cases.

Overview of study methods/analyses

Objectives

The RADARS® SPCP Investigation aims to

- estimate the change in the number of intentional exposure cases for OxyContin® before versus after marketing started for reformulated OxyContin®
- estimate the change in the number of intentional exposure cases for three opioid comparators and compare the magnitude of these changes to OxyContin®

---

[f] Note: The number of poison centers decreased from (b) (4) during the study period.

Reference ID: 3292351

- assess changes in the case fatality rates for OxyContin® and comparator opioids before and after marketing started for reformulated OxyContin®
- compare mortality rates for OxyContin® and comparator opioids before and after marketing started for reformulated OxyContin®

The interim report did not present any findings on changes in case fatality rates or mortality rates.

For the purposes of this serial cross-sectional study, data from RADARS® SPCP is prospectively collected from August 2010 onward, and retrospectively collected prior to August 2010 (see specific dates below).

This investigation's primary and supplemental analyses used varying study periods, which differed from the study periods proposed in this investigation's protocol, as summarized in Table 16. In general, this investigation has two study periods with respect to when marketing started for reformulated OxyContin®. The protocol and one of the interim report's analyses defined a transition period between the two study periods. Both formulations of OxyContin® could be abused during the transition period, and abuse of the original OxyContin® formulation would be less expected after the transition period because fewer prescriptions were dispensed for original OxyContin® after the transition period (see drug utilization data in Figure 40a of Appendix C).

The Reviewer conducted two additional analyses using two study periods and a transition period. The Reviewer defined the study period before marketing started differently for two separate analyses because each analysis used data spanning different time periods. That is, the study period before marketing started was from 4Q2008 to 2Q2010 or from 3Q2009 to 2Q2010. For both analyses, the study period after marketing started was from 1Q2011 to 1Q2012. The Reviewer defined the transition period as 3Q2010-4Q2010.

Table 16: Study periods for the RADARS® System Poison Center Program Investigation, before and after marketing started for reformulated OxyContin®, which occurred in the third quarter of 2010 (3Q2010)

Study period specified by	Study period before marketing started	Transition period	Study period after marketing started
Protocol	**3Q2002-2Q2010**	**3Q2010-4Q2010**	**1Q2011-3Q2013**
Jul 2012 interim report, primary analyses	**4Q2008-3Q2010**		**4Q2010-1Q2012**
Jul 2012 interim report, primary analyses	**4Q2008-2Q2010**	**3Q2010**	**4Q2010-1Q2012**
Jul 2012 interim report, supplemental analyses	**3Q2009-2Q2010**		**3Q2010-1Q2012**
Reviewer's analysis, 1	**4Q2008-2Q2010**	**3Q2010-4Q2010**	**1Q2011-1Q2012**
Reviewer's analysis, 2	**3Q2009-2Q2010**	**3Q2010-4Q2010**	**1Q2011-1Q2012**

The interim report's primary analyses for this investigation examined how the quarter-year rate of cases changed after marketing started for reformulated OxyContin®. The cases examined were associated with the following opioids:

- OxyContin® regardless of formulation
- other prescription opioids

Reference ID: 3292351

According to the protocol, rates were adjusted with either the U.S. population size covered by RADARS® SPCP (according to 3-digit zip codes) or with the number of unique recipients of a dispensed drug (according to 3-digit zip codes), which is a crude measure of the availability of prescriptions dispensed. For example:

Equation 7

$$\text{population-adjusted rate of OxyContin® cases} = \frac{\text{\# cases associated with OxyContin®}}{\text{total population size covered by RADARS® SPCP}}$$

Equation 8

$$\text{recipient-adjusted rate of OxyContin® cases} = \frac{\text{\# cases associated with OxyContin®}}{\text{total unique recipients of dispensed OxyContin®}}$$

The prescription data for the RADARS® SPCP Investigation comes from Vector One National (VONA), a database of SDI Health LLC. VONA can project prescription information (such as, number of unique recipients dispensed a drug) for the U.S., for each U.S. state, and for 3-digit zip codes.

Primary analyses examined changes in rates for the following case types:

- Cases of intentional abuse exposure ("An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect"). Cases of intentional abuse exposure can be considered a population measure of abuse since the catchment area is national and cases are associated with drug abuse; thus the definition of intentional abuse exposure is consistent with the October 2010 Advisory Committee's definition of abuse[b].
- Cases of unintentional therapeutic error ("An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance"). The definition of cases of unintentional therapeutic errors is consistent with the definition of medication error[d] according to the National Coordinating Council on Medication Error Reporting and Prevention.

The protocol for this investigation states that this investigation will examine rates of intentional exposure cases associated with the following routes of administration:

- any route
- any oral route
- inhalation
- injection

However, the interim report did not provide findings on cases of intentional abuse exposure associated with specific routes of administration.

The interim report's supplemental analyses for this investigation examined how the quarter-year rate of cases changed after marketing started for reformulated OxyContin®. The cases examined were associated with the following opioids:

- OxyContin® regardless of formulation

Reference ID: 3292351

- immediate-release (IR) single-entity (SE) oxycodone
- other prescription opioids (immediate-release oxycodone products, hydrocodone, fentanyl, hydromorphone, morphine, oxymorphone, methadone, buprenorphine, tramadol, and tapentadol)

The interim report also presented the count of intentional abuse exposure cases stratified by the following OxyContin® formulations:

- any formulation
- original OxyContin®
- reformulated OxyContin®
- OxyContin® of unknown formulation

The Reviewer noted that none of these exposures capture generic ER oxycodone or other ER oxycodone formulations (such as Canadian OxyContin® or ER oxycodone of unknown formulation), even though they are captured by RADARS® SPCP.

The interim report did not explain why analyses on intentional abuse exposure cases were not stratified by specific OxyContin® formulations.

These supplemental analyses examined rates of cases of

- intentional exposures
- intentional abuse exposures
- unintentional therapeutic errors
- unintentional general exposure

The definition of unintentional general exposures does not include exposures related to abuse or misuse. The definition of intentional exposure cases is not specific to only misuse or abuse, that is, intentional exposure cases also includes cases related to suspected suicide and intentional exposures that were for unknown purposes. (See Appendix E for full list of case exposure definitions).

The interim report's analyses for RADARS® SPCP did not examine cases of intentional misuse exposure, which the National Poison Data System (NPDS) Investigation did examine.

The interim report analyzed rates of cases with two negative binomial regression models that, according to a biostatistics review of this interim report, are generally appropriate for this investigation. Briefly, negative binomial regression was used to estimate the rates of OxyContin®-associated intentional and unintentional exposure cases adjusted for the population in the catchment area, or the number of unique recipients of OxyContin® in the catchment area, as illustrated in Equation 7 and Equation 8. See Biostatistic Reviews for further discussion (35; 36).

The Reviewer also conducted two analyses to determine whether excluding a larger transition period (that is, 3Q2010-4Q2010) appreciably changes the interpretation of this investigation's findings. The Reviewer conducted these additional analyses because the protocol for this investigation had planned to exclude this transition period, but the interim report did not exclude both 3Q2010 and 4Q2010.

The first analysis the Reviewer conducted used data on intentional abuse exposure cases associated with OxyContin® and other prescription opioids from 4Q2008 through 1Q2012, and

Reference ID: 3292351

the second analysis used data on intentional abuse exposure cases associated with Oxycontin® and SE IR oxycodone from 3Q2009 through 1Q2012.

For each opioid, the Reviewer calculated the quarter-year rates of intentional abuse exposure cases (see Equation 7 and Equation 8), using Purdue's data on the number of intentional abuse exposure cases associated with each opioid, the population size covered by the RADARS® System, and the number of unique recipients dispensed each drug. The Reviewer then calculated the average rate of intentional abuse exposure cases per unique recipients dispensed drug for the study periods before and after marketing started for reformulated OxyContin® and the transition period. Finally, the Reviewer tested whether the difference of means between the count and rates of intentional abuse exposure cases were statistically different for each opioid before versus after marketing started for reformulated OxyContin®. The test of the difference of means does not account for autocorrelation among the quarter-year datapoints, and did not compare rates of intentional abuse exposure cases between opioids.

Preliminary findings on overall abuse

Several preliminary findings suggest that, according to poison center cases of intentional abuse exposures, overall abuse of OxyContin® regardless of formulation has been lower since marketing started for reformulated OxyContin® (see Figure 20, Figure 21, Table 17). The interim report's sensitivity analyses, which excluded 3Q2009, found similar results.

Figure 20 illustrates the number of cases associated with OxyContin® regardless of formulation, and also by reformulated OxyContin®, original OxyContin®, and OxyContin® of unknown formulation.

After marketing started for reformulated OxyContin®, the number of intentional abuse exposure cases associated with

- OxyContin® regardless of formulation, decreased with a precipitous drop in 4Q2010 and a stable level thereafter
- reformulated OxyContin®, increased
- original OxyContin®, precipitously dropped in 4Q2010 then decreased more gradually through 3Q2011, when the number of cases associated with original OxyContin® seemed to stabilize
- OxyContin® of unknown formulation, was similar to the number of cases before marketing started

The precipitous drop in OxyContin®-related intentional abuse exposure cases during 4Q2010 seems unexplained given smoother decline in OxyContin® prescriptions dispensed during that period (Figure 40). One such explanation is that some poison centers did not update their software enabling ascertainment of reformulated OxyContin® exposures during this quarter-year.

Reference ID: 3292351

Figure 20: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009-2Q2010) and after (3Q2010-2Q2012) marketing of reformulated OxyContin®, stratified by OxyContin® formulation

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 28" in the workbook RADARS Poison Center Study.xls.

No further analysis explored cases of intentional abuse exposure stratified by OxyContin® formulation.

The interim report's analyses on the rate of intentional abuse exposure cases associated with OxyContin® regardless of formulation found statistically significantly lower rates for OxyContin® after marketing started for reformulated OxyContin® (Figure 21). Specifically, the quarter-year average population-adjusted rate of OxyContin®-related intentional abuse exposure cases was (b) (4) lower after marketing started. Similarly, the quarter-year average recipient-adjusted rate of OxyContin®-related intentional abuse exposure cases was 32% lower after marketing started.

Therefore, the Reviewer noted that the reductions in intentional abuse exposure cases associated with OxyContin® cannot be fully accounted for by declines in OxyContin® prescriptions (see drug utilization in Figure 40a of Appendix C).

Reference ID: 3292351

Figure 21: Rates of intentional abuse exposure cases per population and per unique recipients dispensed opioid, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (4Q2008-3Q2010) and after (4Q2010-1Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and other prescription opioids

(b) (4)

Data source: Figure 24 of the interim report entitled "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"

Reference ID: 3292351

Table 17: Rates of intentional abuse exposure cases per population and per unique recipients dispensed opioid, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (4Q2008-3Q2010) and after (4Q2010-1Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and other prescription opioids

(b) (4)

Data source: Section 4.4.3 of the interim report entitled "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"

†The interim report did not provide all the findings for other prescription opioids.

Compared to changes in intentional abuse exposure rates for other prescription opioids, the reduction in the quarter-year average rate of intentional abuse exposure cases seemed specific to OxyContin®. Specifically, in terms of the quarter-year average population-adjusted rate of intentional abuse exposure cases, cases associated with other prescription opioids did not statistically significantly change after marketing started for reformulated OxyContin® (Table 17). When adjusted for the number of unique recipients dispensed other prescription opioids, the quarter-year average number of intentional abuse exposure cases associated with other prescription opioids statistically significantly decreased by (b) (4).

This (b) (4) reduction was statistically significantly smaller than the 32% reduction in the quarter-year average number of intentional abuse exposure cases associated with OxyContin®.

The Reviewer's analyses yielded similar findings to the interim reports findings (Table 17, Table 18, and Table 19). In particular, for both the Reviewer's analyses and the interim report's analyses, reductions in the rate of intentional abuse exposure cases per unique recipients dispensed drug were observed for OxyContin® and for the comparator opioids – SE IR oxycodone and other prescription opioids. These reductions – in terms of differences in means and relative percent changes – were generally larger for OxyContin® than for the comparator opioids.

Reference ID: 3292351

Table 18: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (4Q2008-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and other prescription opioids

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 24" in the workbook RADARS Poison Center Study.xls.

*Statistically significant difference of means at p=0.05

Reference ID: 3292351

Table 19: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 24" and "Figure 27" in the workbook RADARS Poison Center Study.xls.

*Statistically significant difference of means at p=0.05

According to the Reviewer's analyses, the number and population-adjusted rate of intentional abuse exposure cases associated with other prescription opioids was higher than the number and rate of intentional abuse exposure cases associated with OxyContin® (Table 18, Figure 22a, and Figure 22b).

However, when adjusted for the number of unique recipient dispensed drug, more intentional abuse exposure cases were associated with OxyContin® than with other prescription opioids (Table 18 and Figure 22c). This was true before and after marketing started for reformulated OxyContin®.

Reference ID: 3292351

Figure 22a: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (4Q2008-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and other prescription opioids

(b) (4)

Figure 22b: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (4Q2008-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, adjusted for population size, for OxyContin® regardless of formulation and other prescription opioids

(b) (4)

Figure 22c: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (4Q2008-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, adjusted for unique recipients dispensed drug, for OxyContin® regardless of formulation and other prescription opioids

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 24" in the workbook RADARS Poison Center Study.xls.

The number, population-adjusted rate, and recipient-adjusted rate of intentional abuse exposure cases was consistently higher for OxyContin® compared to SE IR oxycodone (Table 19 and Figure 23a-c).

Figure 23a: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and single-entity (SE) immediate-release (IR) oxycodone

(b) (4)

Reference ID: 3292351

Figure 23b: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and single-entity (SE) immediate-release (IR) oxycodone, adjusted for population size

(b) (4)

Figure 23c: Cases of intentional abuse exposure, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009-2Q2010) and after (1Q2011-2Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation and single-entity (SE) immediate-release (IR) oxycodone, adjusted for unique recipients dispensed drug

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 27" in the workbook RADARS Poison Center Study.xls.

Other preliminary findings

The interim report presented findings on intentional exposure cases, intentional abuse exposure cases, unintentional therapeutic error cases, and unintentional general exposures cases, associated with either OxyContin® regardless of formulation, other prescription opioids, or SE IR oxycodone. These cases were adjusted for population size or unique recipients dispensed drug.

For all four case types, the interim report found lower rates of cases associated with OxyContin® each quarter-year (from 3Q2010 to 1Q2012) than the respective average case rate between 3Q2009 and 2Q2010 (Figure 24a and Figure 24b). While reductions seemed specific to OxyContin® regardless of formulation when adjusting for population size, reductions were also seen for other prescription opioids and SE IR oxycodone after adjusting for unique recipients dispensed each opioid.

Reference ID: 3292351

Purdue asserts that, because reductions in rates of cases per unique recipients dispensed OxyContin® were observed, these additional findings indicate that the reductions in poison center calls of OxyContin® exposures cannot be accounted for by declines in OxyContin® prescriptions dispensed.

As stated previously, the Reviewer noted that reductions in intentional abuse exposure cases associated with OxyContin® cannot be fully accounted for by declines in OxyContin® prescriptions.

Figure 24a: Cases of various types of opioid exposure per population, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009 to 2Q2010, noted in this figure as 'pre-ORF') and after (3Q2010 to 1Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation, other prescription opioids, or single-entity (SE) immediate-release (IR) oxycodone

(b) (4)

Figure 24b: Cases of various types of opioid exposure per unique recipients dispensed opioid, according to calls made to the poison centers participating in the RADARS® System Poison Control Program, before (3Q2009 to 2Q2010, noted in this figure as 'pre-ORF') and after (3Q2010 to 1Q2012) marketing started for reformulated OxyContin®, for OxyContin® regardless of formulation, other prescription opioids, or single-entity (SE) immediate-release (IR) oxycodone

(b) (4)

Data source: Figures 26 and 27 of the interim report entitled "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"

Division of Epidemiology II's Reviewer comments on the preliminary findings on overall abuse

While the above findings could suggest that overall OxyContin® abuse was lower after marketing started for reformulated OxyContin®, the Reviewer noted an unexplained persistence in intentional abuse exposure cases associated with original OxyContin®. Specifically, cases of intentional abuse exposure associated with original OxyContin® did not decline from 3Q2011 to 2Q2012 even though the number of prescriptions dispensed with original OxyContin® during the same timeframe was very low (Figure 40a in Appendix C, and Figure 20). This persistence in intentional abuse exposure cases associated with original OxyContin® is similar to the persistence in abuse of original OxyContin® in the NAVIPPRO™ Investigation (Figure 10).

Although one explanation for this inconsistency may be misclassification of exposures to reformulated OxyContin® as exposures to original OxyContin®, other explanations are possible (such as a long lag time from prescription dispensing to abuse, or diversion of original OxyContin® into the U.S. from markets outside of the U.S.).

The classification of OxyContin® formulation in the RADARS® Investigation may be less reliable than in the NAVIPPRO™ Investigation. Specifically, the Addiction Severity Index – Multimedia Version, which is the data collection tool for the NAVIPPRO™ Investigation,

Reference ID: 3292351

visually aids respondents in identifying the drugs they abused (see Section 3.1.1). On the other hand, callers to poison centers do not have visual aids. Furthermore, this investigation found a prevalent number of unknown OxyContin® formulations (Figure 20).

To better understand possible misclassification of the definition for 'OxyContin®,' this investigation needs to

1) Evaluate intentional abuse exposure cases for all ER oxycodone
2) Evaluate how many cases are related to oxycodone (IR vs. ER formulation not defined)

The Reviewer noted that, although the number and rates of intentional abuse exposure cases associated with OxyContin® did decrease after marketing started for reformulated OxyContin®, the rate of intentional abuse exposure cases per unique recipients dispensed drug was higher for OxyContin® than the comparator opioids (Table 17, Figure 22c, Table 18, Figure 23c, and Table 19).

The Division of Biostatistics VII noted that the findings from this investigation may not be robust when considering different statistical approaches, including using different statistical models, assessing changes in both trend and level of cases, modeling with and without a transition period, and accounting for autocorrelation; for more information, refer to the Biostatistics review (36).

Preliminary findings on route-specific abuse

Although the RADARS® SPCP Investigation is designed to examine cases of exposures associated with specific routes of administration, the July 2012 interim report did not report any route-specific findings. Furthermore, the interim report did not provide any explanation for omitting route-specific findings.

Reference ID: 3292351

3.1.3 National Poison Data System (NPDS)

Data source/data collection

Similar to the RADARS® SPCP Investigation, the NPDS Investigation uses data on exposure calls made to poison control centers. However, unlike the RADARS® SPCP Investigation, which is based on a sample of poison centers in the U.S, this investigation uses data from NPDS, which includes data from all (b) (4) poison centers in the U.S. For each exposure case, Specialists in Poison Information ask callers detailed questions to identify the exposure as accurately as possible, including ascertaining an exposure from a drug product's label, shape, color, and imprint. The Specialists in Poison Information also use a nationally standardized data collection tool to code reasons for exposure reported by callers to poison centers (41). Examples of reasons of exposure include "intentional abuse exposure" and "unintentional general exposure" (see Appendix E for full list of reasons of exposure).

NPDS collects exposure data for various formulations of oxycodone (see Appendix F for the various formulations). Unlike RADARS® SPCP, NPDS does not perform a systematic review of each case's case notes to validate exposures. Since there is no quality control process, there are some reports suggesting up to 50% inaccuracy for product identification for some opioid drug classes.

Overview of study methods/analyses

Similar to the RADARS® SPCP Investigation (see Section 3.1.2), the NPDS Investigation aims to assess changes in exposures – according to calls made to U.S. poison centers – associated with OxyContin® and other opioids before and after marketing started for reformulated OxyContin®.

Methods for the NPDS Investigation were only available in the December 2011 and July 2012 interim reports.

For the purposes of this serial cross-sectional study, data from NPDS is prospectively collected from August 2010 onward, and is retrospectively collected prior to August 2010 (see specific dates below).

The interim report defined two study periods with respect to when marketing started for reformulated OxyContin® (Table 20). Specifically, the study period before marketing started was from the third quarter of 2009 (3Q2009) through the second quarter of 2010 (2Q2010), and the study period after marketing started was from 4Q2010 through 4Q2011. The transition period was 3Q2010. Therefore, unlike the RADARS® SPCP Investigation, the NPDS Investigation did not analyze data from 4Q2008 through 2Q2009 or from 1Q2012 through 2Q2012.

The interim report did not state why the transition periods were defined differently between the RADARS® SPCP Investigation and the NPDS Investigation.

For the additional analyses, the Reviewer defined the transition period as 3Q2010-4Q2010. Both formulations of OxyContin® could be abused during the transition period, and abuse of the original OxyContin® formulation would be less expected after the transition period because

---

[g] Although the number of poison centers in the United States has dropped from (b) (4) during the study period, the coverage of NPDS has remained (b) (4) in the U.S.

Reference ID: 3292351

fewer prescriptions were dispensed with original OxyContin® after the transition period (see drug utilization data in Figure 40a of Appendix C).

Table 20: Study periods for the National Poison Data System Investigation, before and after marketing started for reformulated OxyContin®, which occurred in the third quarter of 2010 (3Q2010)

Study period specified by	Study period before marketing started	Transition period	Study period after marketing started
Jul 2012 interim report	**3Q2009-2Q2010**	**3Q2010**	**4Q2010-4Q2011**
Reviewer's analysis	**3Q2009-2Q2010**	**3Q2010-4Q2010**	**1Q2011-4Q2011**

The interim report presented findings from analyses that examined changes in the quarter-year rate of cases associated with:

- OxyContin® regardless of formulation
- other single-entity (SE) oxycodone prescription products, that is, excluding OxyContin®, but including extended-release generic oxycodone and SE immediate-release oxycodone products
- heroin

Similar to the RADARS® SPCP Investigation, the NPDS Investigation did not assess generic ER oxycodone formulations or other ER oxycodone formulations (such as, Canadian OxyContin®).

Rates were adjusted by either the size of the U.S. Census population or with the national number of prescriptions dispensed, specifically for OxyContin® or other SE oxycodone products.

Analyses in this investigation examined changes in rates for the several case types, but only two case types seem to be relevant to abuse[b] and misuse[c]:

- Cases of intentional abuse exposure ("An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect"). Cases of intentional abuse exposure can be considered a population measure of drug abuse since the catchment area is national and the cases are associated with drug abuse; thus, the definition of intentional abuse exposure is consistent with the October 2010 Advisory Committee's definition of abuse[b].
- Cases of intentional misuse exposure ("An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect"). Cases of intentional misuse exposure can be considered a population measure of drug misuse since the catchment area is national and the cases are associated with drug misuse; thus, the definition of intentional misuse exposure is somewhat consistent with the October 2010 Advisory Committee's definition of misuse[c].

This is the only investigation of the three formal studies of abuse that examines OxyContin® *misuse*.

The other case types examined in this investigation include

- all exposures

Reference ID: 3292351

- intentional exposures - all, suspected suicide, and unknown
- unintentional exposures - all, misuse, general, bite / sting, environmental, food poisoning, occupational, and unknown

See Appendix E for definitions for the above case types.

The investigation also examined cases of adverse reactions (in accordance with labeled, prescribed use) and withdrawal. The interim report did not describe how adverse reactions and withdrawal were defined or collected.

Although the RADARS® SPCP Investigation is designed to examine cases associated with all and specific routes of administration (oral, inhalation, and injection), the NPDS Investigation is currently designed to only examine cases associated with overall (that is, not route-specific) abuse.

Purdue did not conduct statistical analyses testing whether intentional abuse exposure cases and intentional misuse exposure cases associated with OxyContin® or comparator opioids were statistically significantly different before versus after marketing started for reformulated OxyContin®.

Therefore, the Reviewer used data provided by Purdue to test whether changes observed in intentional abuse exposure cases and intentional misuse exposure cases were statistically significant. For each opioid, the Reviewer calculated the quarter-year rates of intentional abuse exposure cases and intentional misuse exposure cases (see Equation 7 and Equation 8). Purdue's data included information on the number of intentional abuse exposure cases associated with each opioid, the population size covered by the RADARS® System, and the number of prescriptions dispensed (OxyContin® and SE oxycodone, only). The Reviewer used these data to calculate the average rate of intentional abuse exposure cases per prescriptions dispensed for the study periods before and after marketing started for reformulated OxyContin® and the transition period. Finally, the Reviewer used a difference of means test to assess whether the count and rates of intentional abuse exposure cases were statistically different for each opioid before versus after marketing started for reformulated OxyContin®. The test of the difference of means does not account for autocorrelation among the quarter-year datapoints, and does not compare rates of intentional abuse exposure cases between opioids.

Preliminary findings on overall abuse and overall misuse

Several preliminary findings suggest that, according to calls made to U.S. poison centers, overall (that is, not route-specific) abuse and misuse of OxyContin® regardless of formulation was lower after marketing started for reformulated OxyContin®.

Specifically, the quarter-year average number of intentional abuse and intentional misuse exposure cases associated with OxyContin® decreased 30% and (b) (4) respectively, after marketing started for reformulated OxyContin® (Table 21). Figure 25a-c suggests that, unlike the increasing trend in number of intentional abuse exposure cases associated with SE oxycodone and heroin, there was a decreasing trend in the number of intentional abuse exposure cases associated with OxyContin®.

Reference ID: 3292351

Table 21: Changes in the quarter-year average number of exposure cases associated with OxyContin®, according to calls made to the U.S. poison centers, before (July 2009 to June 2010) and after (October 2010 to December 2011) marketing of reformulated OxyContin® (noted in the table as "ORF")

(b) (4)

Data source: Table 69 of the interim report entitled "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"

Figure 25a: Cases of intentional abuse exposure, unintentional therapeutic errors, and unintentional general exposures, all associated with OxyContin®, before and after marketing started for reformulated OxyContin® in the third quarter of 2009 (3Q2009)

(b) (4)

Reference ID: 3292351

Figure 25b: Cases of intentional abuse exposure, unintentional therapeutic errors, and unintentional general exposures, all associated with other single-entity oxycodone prescription products (that is, excluding OxyContin®, but included generic extended-release oxycodone), before and after marketing started for reformulated OxyContin® in the third quarter of 2009 (3Q2009)

(b) (4)

Figure 25c: Cases of intentional abuse and unintentional general exposures associated with heroin, before and after marketing started for reformulated OxyContin® in the third quarter of 2009 (3Q2009)

(b) (4)

Data source: Figures 60a-c of the interim report entitled "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"

Analyses conducted by the Reviewer also suggest that intentional abuse and intentional misuse exposure cases associated with OxyContin® were lower after marketing started for reformulated OxyContin® (Table 22 and Figure 26).

Specifically, before marketing of reformulated OxyContin®, the quarter-year average number of intentional misuse exposure cases associated with OxyContin® was (b) (4) cases, and after marketing started for reformulated OxyContin®, this average dropped (b) (4) to (b) (4) cases. However, this difference in means was not statistically significant.

Reference ID: 3292351

Table 22: Cases of intentional abuse exposure and intentional misuse exposure[†], according to calls made to the U.S. poison centers, before (3Q2009-2Q2010) and after (1Q2011-4Q2011) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 60A," "Figure 60B," "Figure 60C," and "Table 69" in the workbook National Poison Data System.xls

[†]The interim report did not provide findings regarding intentional misuse exposure cases associated with other single-entity oxycodone prescription drugs. Heroin is an illicit drug, so there are no intentional misuse exposure cases for heroin.

[‡]The data source did not provide data on intentional misuse exposure cases for 3Q2010

*Statistically significant difference of means at p=0.05

Figure 26: Cases of intentional abuse exposure and intentional misuse[†‡] exposure, according to calls made to the U.S. poison centers, before (3Q2009-2Q2010) and after (4Q2010-4Q2011) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 60A," "Figure 60B," "Figure 60C," and "Table 69" in the workbook National Poison Data System.xls

[†]The interim report did not provide findings regarding intentional misuse exposure cases associated with other single-entity oxycodone prescription drugs. Heroin is an illicit drug, so there are no intentional misuse exposure cases for heroin.

[‡]The data source did not provide data on intentional misuse exposure cases for 3Q2010.

Reference ID: 3292351

The average number of intentional abuse exposure cases associated with OxyContin® regardless of formulation after marketing started for reformulated OxyContin® was statistically significantly lower than before marketing started. Specifically, the quarter-year average number of intentional abuse exposure cases associated with to OxyContin® dropped (b) (4) from (b) (4) cases to (b) (4) cases.

Compared to the opioid comparators of other single-entity (SE) oxycodone prescription products and heroin, the reductions in intentional abuse exposure cases seemed specific to OxyContin® regardless of formulation. Specifically, the quarter-year average number of intentional abuse exposure cases associated with other SE oxycodone products and with heroin was statistically significantly higher after marketing started for reformulated OxyContin® than before marketing started.

However, according to the Reviewer's analyses, the reduction in intentional abuse exposure cases associated with OxyContin® was not statistically significant after adjusting the cases for the number of OxyContin® prescriptions dispensed (Table 23 and Figure 27). Specifically, the prescription-adjusted quarter-year average rate of intentional abuse exposure cases associated with OxyContin® was not statistically significantly lower after marketing started for reformulated OxyContin® (b) (4) intentional abuse exposure cases per 100,000 OxyContin® prescriptions dispensed) compared to before marketing started ((b) (4) intentional abuse exposure cases per 100,000 OxyContin® prescriptions dispensed).

The Reviewer noted that difference of means did not reach statistical significance likely because of the few number of data points.

Meanwhile, the rate of intentional abuse exposure cases per prescription dispensed did not significantly change for other single-entity (SE) oxycodone products. Before and after marketing started for reformulated OxyContin®, there were approximately (b) (4) intentional abuse exposure cases per 100,000 prescriptions dispensed for other SE oxycodone products.

Table 23: Prescription-adjusted rate of cases of intentional abuse exposure, according to calls made to the U.S. poison centers, before (3Q2009-2Q2010) and after (4Q2010-4Q2011) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 60A," "Figure 60B," "Figure 65A," and "Figure 65B" in the workbook National Poison Data System.xls

*Statistically significant difference of means at p=0.05

Reference ID: 3292351

Figure 27: Prescription-adjusted rate of cases of intentional abuse exposure, according to calls made to the U.S. poison centers, before (3Q2009-2Q2010) and after (1Q2011-4Q2011) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheets "Figure 60A," "Figure 60B," "Figure 65A" and "Figure 65B" in the workbook National Poison Data System.xls

Note: Because of the limited number of data points, no statistical test was performed on the trend of prescription-adjusted rate of cases of intentional abuse exposure associated with OxyContin® or other single-entity oxycodone.

The Reviewer found that, adjusted for a measure for the availability of each opioid (that is, prescriptions dispensed), the rate of intentional abuse exposure cases was similar between OxyContin® and other SE oxycodone products (Figure 27). This finding is in contrast with the RADARS® SPCP Investigation, which found that the rate of intentional abuse exposure cases – also adjusted for a measure of the availability of each opioid (that is, unique recipients of dispensed opioid) – was higher for OxyContin® than for SE IR oxycodone (see Figure 23c). This discrepancy may reflect the slightly different choice of comparator, the different choice of adjustment, or exposure validation procedures in the RADARS® SPCP Investigation, but not in the NPDS Investigation.

Division of Epidemiology II Reviewer comments on the preliminary findings on overall abuse

The decrease in the unadjusted quarter-year average of intentional abuse exposure cases associated with OxyContin® after marketing started for reformulated OxyContin® was statistically significant, but the decrease in the prescription-adjusted quarter-year average rate was not statistically significant. However, this lack of statistical significance for the change in the prescription-adjusted quarter-year average rate of intentional abuse exposure cases associated with OxyContin® may reflect the small number of datapoints that were analyzed (4 datapoints for each study period before and after marketing started for reformulated OxyContin®).

If possible, modifications to the NPDS Investigation could make this investigation more comparable to, and interpretable in the context of, the RADARS® SPCP Investigation. The protocol for the NPDS Investigation should be modified to:

- incorporate analyses on mortality rate and case fatality rate – specifically, case fatality rate for intentional abuse exposure cases and intentional misuse exposure cases – to make assessments of clinical outcomes in Purdue's postmarketing study program more robust
- stratify cases of intentional abuse exposures and intentional misuse exposures associated with OxyContin® by OxyContin® formulation, to help assess intentional abuse or misuse exposure cases specifically associated with reformulated OxyContin®

Reference ID: 3292351

- redefine the comparator, ‘other single-entity (SE) oxycodone’ as ‘SE immediate-release (IR) oxycodone’ to ensure that generic SE extended-release oxycodone products are not included in this comparator

Similar to as was noted for the RADARS® SPCP Investigation, the Division of Biostatistics VII noted that the findings from this investigation may not be robust when considering different statistical approaches; for more information, refer to the Biostatistics Review (36).

Reference ID: 3292351

3.2 OVERVIEW OF METHODS AND PRELIMINARY FINDINGS FOR EIGHT SUPPLEMENTAL INVESTIGATIONS

3.2.1 National Surveys Investigation

Data source/data collection

This investigation is a multi-year cross-sectional study that uses survey data from the following surveys:

- National Survey on Drug Use and Health (NSDUH)
- Monitoring the Future (MTF)
- RADARS® System College Survey (RADARS-CS)

NSDUH, which is maintained by the Substance Abuse and Mental Health Administration (SAMHSA), collects nationally representative annual data on the characteristics of non-medical pharmaceutical opioid use among children, young adults, and older adults. MTF, which is maintained by the Survey Research Center at the University of Michigan, collects nationally representative annual data on past-year non-prescribed drug use among 8th, 10th, and 12th graders. For each of the three college semesters per year, RADARS-CS collects data on self-reported non-medical drug use in the past three months among college students. The interim reports and protocol do not provide sufficient evidence that the RADARS-CS sample is nationally representative.

None of the surveys distinguish between drug abuse and drug misuse, according to the definitions of abuse[b] and misuse[c] that were used at the October 2010 Advisory Committee. Therefore, although the interim report infers that the results are specific to abuse, the results could reflect both abuse and misuse.

Overview of methods/analyses

The National Surveys Investigation aims to:

- estimate the prevalence of, and changes in the prevalence of, the use of OxyContin® and other opioids for non-medical purposes before and after marketing started for reformulated OxyContin®
- estimate the proportion of college students who reported non-medical use of OxyContin® via alternative routes of administration (injection, snorting, or chewing) in the three months prior to survey administration, before and after marketing started for reformulated OxyContin®
- estimate the prevalence of the stages of non-medical OxyContin® use (recent onset use, persistent use, and opioid dependence according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition) before and after marketing started for reformulated OxyContin®

The interim report did not provide findings for the second and third objectives.

For all three surveys, the protocol did not state what the opioid comparators would be.

For the RADARS-CS survey, the interim report presented findings on non-medical use of

- OxyContin® regardless of formulation

Reference ID: 3292351

- immediate-release (IR) oxycodone prescription products
- other prescription opioids, including oxycodone, hydrocodone, buprenorphine, fentanyl, morphine, hydromorphone, and methadone

The protocol defined two study periods with respect to when marketing started for reformulated OxyContin®. Specifically, the study period before marketing started was from August 2004 to August 2010, and the study period after marketing started was from August 2010 to August 2012. The protocols and the interim reports did not state whether annual NSDUH and MTF data for year 2010 were to be included in the study period before marketing started for reformulated OxyContin®, or after marketing started.

For the RADARS®-CS survey, the interim report presented the second and third college semesters as part of the study period that occurred after marketing started for reformulated OxyContin®.

Purdue used negative binomial regression to estimate the rate of non-medical OxyContin® use per 100,000 college students for each college semester.

Preliminary results

Data from RADARS-CS showed that prevalence of non-medical OxyContin® use did not change after marketing started for reformulated OxyContin® (Figure 28). For each semester from the second semester of 2010 (noted in Figure 28 as 3Q2010) through the first semester of 2012 (noted as 1Q2012), the estimated population-adjusted rate of non-medical OxyContin® use was not statistically different than the estimated population-adjusted average rate of non-medical OxyContin® use from the second semester of 2009 through the first semester of 2010.

Similarly, according to MTF, the prevalence of non-medical OxyContin® use did not appreciably change after marketing started for reformulated OxyContin® (Figure 29). Among 8th, 10th, and 12th graders in year 2011, the prevalence of non-medical OxyContin® use (b) (4) for 8th graders, (b) (4) for 10th graders, and (b) (4) for 12th graders) was only slightly less than or equal to the prevalence of OxyContin® use in years 2009 (b) (4) and (b) (4), respectively) and 2010 (b) (4) and (b) (4), respectively).

Figure 28: Prevalence of non-medical prescription opioid use among college students, according to the RADARS® System College Survey, by opioid

(b) (4)

Source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 30" in the workbook RADARS College Survey Study.xls

Reference ID: 3292351

Figure 29: Prevalence of non-medical OxyContin® use among 8th, 10th, and 12th graders, according to the Monitoring the Future survey

(b) (4)

Data source: Table 31 in the interim report entitled "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"

Note: The Reviewer has treated year 2010 as a transition period.

Division of Epidemiology II Reviewer comments

Although the National Surveys Investigation assesses prevalence of non-medical use of OxyContin®, it is not considered a formal study because the number of data points generated by these surveys is too small to assess changes in the level and trend in non-medical OxyContin® use. Specifically, as is discussed further in Section 6, the Reviewer generally recommends using 3 to 5 years of data after marketing started for reformulated OxyContin®. Therefore, the annual NSDUH and MTF data and the quarter-years of missing data in RADARS-CS preclude a sufficiently powered trend analysis.

This investigation should evaluate whether NSDUH's quarter-year national estimates of non-medical OxyContin® use are sufficiently precise to investigate quarter-year trends in non-medical OxyContin® use. If so, then the NSDUH component of this investigation could be a formal study of abuse with more data points to assess level and trend in the prevalence of non-medical OxyContin® use. Ideally, the Reviewer recommends 3 to 5 years of (quarter-year) data for a formal study of reformulated OxyContin®.

Observing statistically significant changes in non-medical OxyContin® use may be difficult in this investigation. Specifically, the populations studied are not generally at high risk of opioid abuse, so changes in non-medical OxyContin® use among the higher risk subjects in these populations would be muted by the lower risk subjects. Furthermore, past-use of OxyContin® could include experimental use – which the Reviewer assumes to be experimental oral use.

In the Reviewer's opinion, this investigation's findings for the RADARS-CS Survey would likely need to be stratified by route of administration to observe reductions in non-medical OxyContin® use.

Reference ID: 3292351

3.2.2 Kaiser Permanente Health System Investigation

Data source/data collection

The Kaiser Permanente (KP) Health System Investigation uses electronic healthcare data from the KP Northwest Health System and the KP Northern California Health System. These data are prospectively collected from August 2010 onward, and retrospectively collected prior to August 2010 (see specific dates below).

The KP Health System electronically collects demographic and medical record information (such as inpatient stays, outpatient medical visits, dispensed prescriptions, laboratory tests, imaging data, and claims made to KP from health care providers outside of the KP network) for KP health plan members. Access to electronic medical records for all members is a potential strength of this investigation.

Overview of methods/analyses

The Kaiser Permanente (KP) Health System Investigation, a cohort study with a qualitative research component, aims to:

- estimate and compare the rates of opioid overdose and poisoning events among patients prescribed OxyContin® and comparator opioids, and among patients not prescribed these opioids, before and after marketing started for reformulated OxyContin®
- assess changes in the trend of opioid overdose and poisoning rates among patients prescribed OxyContin® and comparator opioids, and among patients not prescribed these opioids, before and after marketing started for reformulated Oxycontin®
- conduct qualitative research on a subset of patients who experienced opioid and overdose and poisoning events

The protocol defined two study periods for each of the three objectives above with respect to when marketing started for reformulated OxyContin® (Table 24). In brief, the study period before marketing started was up to seven years prior to August 2010, and the study period after marketing started was up to two and half years after August 2010. The study periods were divided into half-year intervals, so marketing started for reformulated OxyContin® during the second half of 2010 (2H2010).

Reference ID: 3292351

Table 24: Study periods for the Kaiser Permanente Health System Investigation, before and after marketing started for reformulated OxyContin® in the second half of 2010 (2H2010), by objective

Objective	Study period before marketing started	Study period after marketing started
To estimate and compare the rates of opioid overdose and poisoning events among patients prescribed OxyContin® and comparator opioids, and among patients not prescribed these opioids, before and after marketing started for reformulated OxyContin®	2H2008-1H2010	2H2010-1H2011
To assess changes in the trend of opioid overdose and poisoning rates among patients prescribed OxyContin® and comparator opioids, and among patients not prescribed these opioids, before and after marketing started for reformulated Oxycontin®	2H2003-1H2010	2H2010-2H2012
To conduct qualitative research on a subset of patients who experienced opioid and overdose and poisoning events	Prior to 2H2010	From 2H2010 onward

To identify cases of opioid poisonings and cases of opioid overdoses, this investigation used codes from three medical coding systems: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), ICD-10, and the Healthcare Common Procedure Coding System (HCPCS) (See Appendix G for case definitions). These case definitions build upon case definitions mentioned in the medical literature (42; 43).

The case definition for opioid poisonings required the presence of at least one ICD-9-CM code or ICD-10 code associated with opioid poisonings. Examples include the ICD-9-CM code 965.00 for 'poisoning by opiates' and the ICD-10 code T40.3 for 'poisoning by methadone.' The case definition for opioid overdoses required two codes: at least one ICD-9-CM or ICD-10 code indicating an opioid-related adverse effect, and at least one ICD-9-CM code indicative of overdose. Examples include the ICD-10 code Y45.0 for 'adverse effects of opioids and related analgesics' and the HCPCS code J2310 for 'injection, naloxone hydrochloride.'

This investigation has a validation stage to ascertain whether the case definitions for opioid overdose and opioid poisoning are valid. The validation stage has started, but is not finished. During the validation stage, trained research clinicians use a standardized chart audit form to obtain information from approximately (b) (4) medical charts associated with a sample of suspected opioid overdose and poisoning occurring during 2H2008-1H2012. Although the criteria for selecting cases to validate initially differed between the two KP health systems, the selection criteria will eventually be uniform between the sites and include a sufficient number of cases to determine the validity of the case definitions. Specifically, all cases identified in the KP Northwest Health System will be validated, and all cases associated with extended-release (ER) oxycodone and a proportional sample of events related to other opioids will be validated.

The information obtained from the chart audits will help determine the following:

- the causal opioid
- substances (such as medications, alcohol, and illicit substances) contributing to the event
- details of prescriptions dispensed, including dose
- route of administration contributing to the event
- source of procurement for each substance involved

Reference ID: 3292351

- evidence of misuse, abuse, or over-administration of each substance
- treatment with naloxone hydrochloride
- whether the event was related to suicide (including a completed and attempted suicide as well as suicidal ideation)
- whether the event was miscoded or related to an anesthetic procedure
- whether the event was an opioid-related adverse event, defined as an event that was related to opioid use but did not require intervention beyond adjusting or discontinuing medication to resolve the event (for example, sensitivity reaction to properly administered medication)

The Reviewer assumed that an adverse event that did require medical intervention beyond adjusting or discontinuing medication (such as use of naloxone hydrochloride) was considered an opioid overdose and poisoning case.

The main proposed analyses have not been started because the investigation is still in its validation stage.

Preliminary results: Validation stage

According to the case definition for opioid overdoses, there were (b) (4) opioid overdose cases in total within the KP Northwest Health System during 2H2008-1H2012, but validation of medical charts associated with these cases revealed that the case definition for opioid overdose was not specific for overdose events. Specifically, (b) (4) of the (b) (4) cases were determined to not be opioid overdoses because cases either

- did not have medical chart information for the date of the event,
- were related to anesthesia or post-surgical pain management,
- were miscoded by medical coding staff, and/or
- were misidentified (that is, both codes required for the case definition were correct, but were unrelated)

Of the remaining (b) (4) cases, (b) (4) of the (b) (4) cases) were determined to be opioid-related adverse events, and the other (b) (4) were determined to be opioid overdoses. Because of the lack of adequate positive predictive value in the opioid overdose case definition, the opioid overdose case definition was dropped from the investigation.

To date, the investigators have completed medical record abstractions and audits of medical charts for (b) (4) cases associated with opioid poisonings, as identified with the case definition of opioid poisoning. These (b) (4) cases include (b) (4) opioid poisoning cases within the KP Northwest Health System and (b) (4) opioid poisoning cases within the KP Northern California Health System. The validation of medical records associated with these cases revealed that (b) (4) of cases identified with the case definition for opioid poisonings are correctly identified as opioid poisonings. However, these cases are not a random sample from the pool of eligible cases. Therefore, although further analyses were done on these cases, the Reviewer believes that it would be premature to interpret the findings.

Analysis of the percentage of members dispensed brand-name ER oxycodone (that is, OxyContin®) versus generic ER oxycodone shows that dispensings of generic ER oxycodone were still prevalent in the KP Health System from 2004 to 2010 (Figure 30). Specifically, generic ER oxycodone prescriptions dominated the ER oxycodone market in the KP Health System

Reference ID: 3292351

beginning in 2005. The percent of members dispensed generic ER oxycodone dropped below (b) (4) by August 2008, to roughly (b) (4) by August 2009, and to roughly (b) (4) by August 2010.

Figure 30: Percent of people in the Kaiser Permanente Health System dispensed extended-release (ER) oxycodone that was either generic (that is, 'oxycodone ER') or brand (that is, OxyContin®)

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Oct 22, 2012, specifically, Figure 1

While the results of the KP Health System Investigation may be informative with respect to assessing the association between introduction of reformulated OxyContin® to the market and opioid poisonings, it is not currently considered a formal study of abuse because exactly how the clinical outcomes will be attributed to abuse (rather than to other behaviors) is not clear. The investigation should assess whether the clinical outcomes are attributable to abuse in order to develop a more relevant, abuse-related measure in the assessment of abuse-deterrence. In addition, it is difficult to determine the relative importance of this investigation or how the results should be interpreted. The investigators did not provide data on the size of the base study population or the baseline prescribing levels, both which are, according to the investigators, proprietary to KP. Without these key pieces of data, it is not possible to place these results in context either within the KP Health System or other, similar populations.

Reference ID: 3292351

3.2.3 RADARS® System Drug Diversion Program Investigation

Data source/data collection

The RADARS® System Drug Diversion Program collects quarter-year data on pharmaceutical diversion cases reported to or investigated by approximately (b) (4) law enforcement diversion units or regulatory boards located across all 50 states. These (b) (4) investigators and regulatory agencies, which are a convenience sample of all law enforcement and regulatory agencies that could provide diversion data, provide diversion and street price data to RADARS® using the National Drug Diversion Survey and Street Price Questionnaire.

Purdue hypothesizes that one method of demonstrating the effectiveness that the reformulation of OxyContin® has on minimizing abuse will be to show that the new formulation is less desirable for abuse, as indicated by reductions in new diversion cases and street prices for OxyContin®. Therefore, this investigation examines new diversion cases and the average street price for OxyContin® as surrogate measures of OxyContin® abuse.

Overview of methods/analyses

The primary aim of the RADARS® System Drug Diversion Program Investigation, a pre-post descriptive investigation, is to compare the change in the number of drug diversion cases associated with OxyContin® before and after marketing started for reformulated OxyContin® to the change in the number of drug diversion cases associated with the three opioid comparators

The secondary aim of this investigation is to compare the change in the average street price of OxyContin® before and after marketing started for reformulated OxyContin® to the change in the average street price for the same three comparators assessed for the primary aim

Therefore, the Reviewer noted that this investigation does not assess actual opioid abuse, including route-specific abuse.

The three opioid comparators mentioned in this investigation's protocol include

- immediate-release (IR) single-entity (SE) oxycodone prescription products
- IR hydrocodone-acetaminophen
- fentanyl transdermal patches plus methadone

The interim report did not present findings on analyses regarding two comparators listed in the protocol: IR hydrocodone-acetaminophen and the comparator of fentanyl transdermal patches plus methadone.

Instead, the interim report compared OxyContin® to

- other prescription opioids
- IR SE oxycodone prescription products

The protocol, the interim report, and the Reviewer differed in their definitions of the study periods occurring before and after marketing started for reformulated OxyContin® (Table 25). In particular, although the interim report presented findings for analyses that only examined diversion data from 3Q2009 through 3Q2010 (which was the study period before marketing started) and 4Q2010 through 1Q2012 (which was the study period after marketing started), diversion data for 4Q2008 through 2Q2009 was also presented, but not analyzed. In addition, data submitted by Purdue for an information request by the FDA contained data through 2Q2012, one quarter-year more than was analyzed for the interim report.

Reference ID: 3292351

For the purposes of this review, the Reviewer has redefined the study period before marketing started as 4Q2008-2Q2010, and the study period after marketing started as 1Q2011-2Q2012. The Reviewer also defined a transition period (3Q2010-4Q2010) that occurred between the study periods before and after marketing started for reformulated OxyContin®. During this transition period, diversion of original OxyContin® was likely. However, after this transition period, fewer prescriptions were dispensed for original OxyContin® (see drug utilization analysis in Figure 40a in Appendix C).

Table 25: Study periods for the RADARS® System Drug Diversion Program Investigation

Timeframe with respect to marketing of reformulated OxyContin®	Inclusion of timeframe in analyses?	Protocol	July 2012 Interim Report	Reviewer
Before marketing started	No		4Q2008-2Q2009	
Before marketing started	Yes	1Q2002-3Q2010	3Q2009-3Q2010	4Q2008-2Q2010
Transition period	No			3Q2010-4Q2010
After marketing started	Yes	4Q2010-2Q2013	4Q2010-1Q2012	1Q2011-2Q2012

The interim report presented findings on the number of diversion cases and the rate of diversion cases per size of the U.S. population covered by the RADARS® System Drug Diversion Program, according to 3-digit zip codes.

For the interim report, negative binomial regression was used to estimate the population-adjusted rates of diversion cases and to compare the percent change for each quarter-year rate from 3Q2010-1Q2012 to the average rate during the period before marketing of reformulated OxyContin®.

The Reviewer noted that the analyses conducted for the interim report do not use all available data to answer whether the number and rate of diversion cases statistically significantly changed after marketing started for reformulated OxyContin®.

Therefore, the Reviewer used data, which Purdue provided, on number of diversion cases and population size covered by the RADARS® System to calculate the average population-adjusted rate of diversion cases for the study periods before and after marketing started for reformulated OxyContin®. Then, using a difference of means test, the Reviewer assessed whether the average numbers and rates of diversion cases before versus after marketing started for reformulated OxyContin® were statistically significantly different.

One abstract had the most current findings on average street prices, calculated as a geometric mean. The geometric mean street price accounts for potential skew in street prices.

Preliminary findings

The interim report found that the number of diversion cases associated with either OxyContin® or other prescription opioids decreased after marketing started for reformulated OxyContin® (Figure 31). The number of diversion cases associated with OxyContin® ranged from (b) (4) during 4Q2008-3Q2010, and from (b) (4) during 4Q2010-1Q2012. Meanwhile, the number of diversion cases associated with other prescription opioids ranged from (b) (4) during 4Q2008-3Q2010, and from (b) (4) during 4Q2010-1Q2012.

Reference ID: 3292351

Figure 31: Drug diversion cases associated with OxyContin®, other single-entity (SE) immediate-release (IR) oxycodone prescription products, and other prescription opioids, according law enforcement diversion units and regulatory agencies providing data to RADARS® System Drug Diversion Program, before (4Q2008-2Q2010) and after (3Q2010-2Q2012) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 33" in the workbook RADARS Drug Diversion Study.xls

Note: The Reviewer defined the transition period as 3Q2010-4Q2010. The interim report did not define a transition period. See Table 25.

The interim report also found that, compared to the average population-adjusted rate of diversion cases associated with OxyContin® during 3Q2009-3Q2010, the population-adjusted rate of diversion cases associated with OxyContin® was lower most quarter-years from 4Q2010 to 1Q2012 (Figure 32). The confidence intervals in Figure 32 show that the population-adjusted rate of diversion cases associated with OxyContin® did not reach statistical significance until 1Q2011.

Compared to the comparators of SE IR oxycodone and other prescription opioids, the reductions in the population-adjusted rate of diversion cases seemed specific to OxyContin®. That is, for most quarter-years from 3Q2010 to 1Q2012, the population-adjusted rate of diversion cases associated with either SE IR oxycodone or other prescription opioids was not statistically significantly different than their average rates in 3Q2009-3Q2010.

Reference ID: 3292351

Figure 32: Percent change in the population-adjusted rate of drug diversion cases compared to the average population-adjusted rate of drug diversion cases in the period from the third quarter of 2009 (2009Q3) to the second quarter of 2010 (2010Q3), by opioid

(b) (4)

Data source: Figure 33 in the interim report entitled "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"

Note: ORF = OxyContin® reformulated

Note: IR oxycodone refers to single-entity immediate-release oxycodone

The Reviewer's analyses found that the average number of diversion cases associated with OxyContin® statistically significantly decreased after marketing started for reformulated OxyContin® (Figure 31, Table 26, and Figure 33). Specifically, the average number of diversion cases associated with OxyContin® was (b) (4) from 4Q2008 through 2Q2010 (that is, the study period before marketing started for reformulated OxyContin®), and the average number of diversion cases associated with OxyContin® was (b) (4) from 1Q2011 to 2Q2012 (that is, the study period after marketing started). Meanwhile, the average number of diversion cases for SE IR oxycodone prescription products and other prescription opioids did not statistically significantly change.

The population-adjusted average number of diversion cases associated with OxyContin® also statistically significantly decreased from an average of (b) (4) diversion cases per 1,000,000 population before marketing started for reformulated OxyContin®, to an average of (b) (4) diversion cases per 1,000,000 population after marketing started. Meanwhile, the population-adjusted average number of diversion cases associated with SE IR oxycodone prescription products or other prescription opioids before marketing started (b) (4) diversion cases associated with SE IR oxycodone per 1,000,000 population and (b) (4) diversion cases associated with other prescription opioids per 1,000,000 population) was not significantly different than the population-adjusted average number of diversion cases after marketing started (b) (4) diversion cases per 1,000,000 population and (b) (4) diversion cases per 1,000,000 population, respectively).

Reference ID: 3292351

Figure 33: Population-adjusted number of drug diversion cases associated with OxyContin®, other single-entity (SE) immediate-release (IR) oxycodone prescription products, and other prescription opioids, according law enforcement diversion units and regulatory agencies providing data to RADARS® System Drug Diversion Program, before (4Q2008-2Q2010) and after (3Q2010-2Q2012) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 33" in the workbook RADARS Drug Diversion Study.xls

Table 26: Drug diversion cases associated with OxyContin®, other single-entity (SE) immediate-release (IR) oxycodone prescription products, and other prescription opioids, according law enforcement diversion units and regulatory agencies providing data to RADARS® System Drug Diversion Program, before (4Q2008-2Q2010) and after (3Q2010-2Q2012) marketing started for reformulated OxyContin®, by opioid

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 33" in the workbook RADARS Drug Diversion Study.xls

*Statistically significant difference of means at p=0.05

The abstract with updated findings on average street prices stated that, after marketing started for reformulated OxyContin®, the geometric mean street price per milligram (mg) of reformulated OxyContin® was statistically significantly lower than the geometric mean street price per mg of original OxyContin® formulation (Table 27). Specifically, in 3Q2010-3Q2011, the mean street price of original OxyContin® formulation was $0.85 per mg, 95% confidence interval [$0.80, $0.91], and the mean street price of reformulated OxyContin® was 21% lower at $0.68 per mg, 95% CI [$0.62, $0.75].

Reference ID: 3292351

Table 27: Geometric mean street price per milligram of OxyContin®, according law enforcement diversion units and regulatory agencies providing data to RADARS® System Drug Diversion Program, before (1Q2010) and after (3Q2010-3Q2011) marketing started for reformulated OxyContin®, by OxyContin® formulation

Quarter-year	Geometric mean street price [95% CI] per mg of opioid	
	Original OxyContin® formulation	Reformulated OxyContin®
1Q2010	$0.80 [$0.74, $0.86]	
3Q2010-3Q2011	$0.85 [$0.80, $0.91]	$0.68 [$0.62, $0.75]

Data source: Exhibit 8 of document 0001 of docket FDA-2012-P-0760

Division of Epidemiology II Reviewer comments

Understanding how this investigation's preliminary findings should be interpreted is not as clear cut as assuming that diversion cases associated with OxyContin® reflect desirability of OxyContin® for abuse. First, the actual number of, or a surrogate measure of, the illegal supply of OxyContin® and comparator opioids would be essential to put the results for diversion cases into context. It is unlikely that an accurate measure of diverted opioids exists, so whether changes in the number of diversion cases reflect changes in demand, in supply, both demand and supply of OxyContin®, or possibly other factors cannot be determined.

Second, the amount of OxyContin® being captured in diversion cases is not provided, and whether RADARS® System Drug Diversion Program captures this information is unknown. Possible measures of the amount of OxyContin® being captured in diversion cases include number of tablets captured, overall and stratified by milligram strength. Therefore, the assumption that the number of diversion cases associated with OxyContin® reflects the true amount of OxyContin® being caught in diversion cases was not tested.

Third, the formulation of OxyContin® captured in diversion cases is not provided because RADARS® System does not stratify diversion cases by specific OxyContin® formulations. Therefore, the length of time original OxyContin® is distributed illegally is unknown, and the percent of diversion cases associated with either original or reformulated OxyContin® - or both – is also unknown.

Similarly, assuming that street price is a valid measure of the desirability of OxyContin® for abuse is not clear cut. Again, the actual number of or a surrogate measure of the illegal supply of OxyContin® and comparator opioids would be essential to put results for street prices into context. In addition, fewer prescriptions were dispensed for higher dosages of OxyContin® (see Section 3.2.7), so the lower prices may reflect changes in the dosage strength available for illegal sale.

Drug diversion and street prices may reflect the demand for OxyContin® for abuse or misuse, but exactly how changes in drug diversion events and street prices correspond to changes in behavioral outcomes (such as drug abuse) or clinical outcomes (such as overdoses) is unclear. The Reviewer also noted that, paradoxically, diversion cases necessarily prevent the opioids that were captured in the cases from being abused. This investigation has not addressed how it will reconcile the effect of diversion cases on future abuse, given that diversion cases are also considered a surrogate measure of abuse.

According to analyses conducted by the Division of Biostatistics VII, findings on the population-adjusted rate of OxyContin® diversion cases may not be robust when considering a different

Reference ID: 3292351

analytical approach, such as modeling changes in both the level and trend of the population-adjusted rate; for more information, refer to the Biostatistics review (36).

Reference ID: 3292351

3.2.4 Doctor Shopping Investigation

Data source/data collection

Although this investigation was originally designed to only use data from both Ohio and Connecticut's prescription drug monitoring programs, the interim report presented findings that used data from:

- Ohio's prescription drug monitoring program
- IMS LRx

Prescription drug monitoring programs, which are authorized in 48 states, are statewide electronic databases of dispensed prescriptions (including controlled substances), which are linked to unique individuals (44). The database structure, program's location within state government agencies, and information collected vary from state to state. Querying the databases can help identify potential drug prescription abuse/misuse, deter and prevent prescription drug abuse, and help identify individuals who may be in need of treatment for substance abuse problems.

IMS LRx is a database that consists of longitudinal, de-identified person-level prescription data from a sample of the IMS Health retail and mail order universe. This database includes data originating from retail and mail service pharmacies including the IMS Health data supplier panel. The coverage of IMS LRx is (b) (4) of the whole universe of prescriptions dispensed by retail and mail order pharmacies.

Overview of methods/analyses

The Doctor Shopping Investigation aims to characterize and compare the counts and rates of doctor-shopping for OxyContin® and comparator opioids before and after marketing started for reformulated OxyContin®.

Therefore, the Reviewer noted that this investigation does not assess actual opioid abuse, or route-specific abuse.

For the purposes of this cross-sectional study, data from IMS LRx and prescription drug monitoring programs are prospectively collected from August 2010 onward, and retrospectively collected prior to August 2010 (see specific dates below).

This study's protocol defined two study periods with respect to when marketing started for reformulated Oxycontin®. Specifically, the study period before marketing started was from the second half of 2007 (2H2007) to the first half of 2010 (1H2010), and the study period after marketing started was from 2H2010 to 2H2012.

For the interim report's analyses of data from Ohio's prescription drug monitoring program, the study period before marketing started was from 1H2009 through 2H2010, and the study period after marketing started was 1H2011 only.

For analyses of data from IMS LRx, the study period before marketing started was from 2H2009 through 1H2010, and the study period after marketing started was from 1H2011 through 2H2011 (Table 28).

Reference ID: 3292351

Table 28: Study periods for the Doctor Shopping Investigation, before and after marketing started for reformulated OxyContin®

Study period specified by	Data Source	Study period before marketing started	Transition period	Study period after marketing started
Protocol	Ohio or Connecticut Prescription Drug Monitoring Programs	2H2007-1H2010		2H2010-2H2012
Jul 2012 interim report	Ohio Prescription drug Monitoring Program	1H2009-2H2010		1H2011
Jul 2012 interim report	IMS LRx	2H2009-1H2010		1H2011-2H2011

Analyses performed with Ohio's prescription drug monitoring program included all individuals who filled prescriptions in Ohio.

For each 6-month time interval, analyses performed with IMS LRx data only included data from individuals who had at least one prescription filled within three months prior to each 6-month time interval and at least one OxyContin® prescription filled during the 6-month time interval. Additionally, analyses performed with IMS LRx data only included data from pharmacies that provided dispensing data for each 6-month time interval and its respective 3-month look-back period.

In general, the interim report for this investigation defined doctor-shopping based on an algorithm of the number of pharmacies (from 2 to 5 pharmacies, or from 2+ to 5+ pharmacies) and number of physicians (from 2 to 5 physicians, or from 2+ to 5+ physicians) an individual visits to fill opioid (specifically, OxyContin®) prescriptions within a 6-month time frame. Because of the many variations in number of pharmacies and physicians that could be used to identify doctor-shopping, there are 64 possible definitions for doctor-shopping:

- Definitions based on a specific number of pharmacies and a specific number of physicians (for example, 4 pharmacies and 5 physicians): 16 doctor-shopping definitions
- Definitions based on a number range for pharmacies and number range for physicians (for example, 2+ pharmacies and 3+ physicians): 16 doctor-shopping definitions
- Definitions based on a specific number of pharmacies and a number range for physicians, or vice versa (for example, 3+ pharmacies and 2 physicians): 32 doctor-shopping definitions

The protocol stated that, for primary analyses, doctor-shopping would be an individual's use of 2+ pharmacies and 2+ physicians to fill OxyContin® prescriptions. Sensitivity analyses were to use other variants of the number of pharmacies and physicians in order to identify doctor-shopping individuals.

The July 2012 interim report used 2+ prescribers and 3+ pharmacies as the definition of doctor shopping for the IMS LRx analyses because changes in doctor-shopping became more pronounced with this definition in another study of doctor-shopping (45). However, the Reviewer noted that Purdue has not verified whether this definition of doctor-shopping has predictive or concurrent validity for actual doctor-shopping or abuse.

The July 2012 interim report did not have a set a definition of doctor-shopping for the Ohio prescription drug monitoring program analyses.

Reference ID: 3292351

With regard to analyses performed with data from Ohio's prescription drug monitoring program, the investigators did the following:

- Determined the number of different pharmacies and physicians used by each individual to fill all their OxyContin® prescriptions in each 6-month time interval
- Applied the algorithm described above to determine the number of individuals who could be considered doctor-shopping for OxyContin®
- Divided the number of doctor-shopping individuals by the number of OxyContin® prescriptions dispensed in Ohio during the 6-month time interval

The investigators did the following with data from IMS LRx:

- Identified occurrences of an OxyContin® prescription being filled before the end date (dispensing date + days supply) of another opioid prescription
- Determined how many opioid prescriptions overlap on the date OxyContin® was dispensed (that is, there could be more than two prescriptions overlapping for each occurrence of overlapping prescriptions)
- Counted the number of pharmacies and physicians used to fill each of the overlapping prescriptions
- Applied the algorithm described above to determine the number of events that could be considered events of doctor-shopping for OxyContin®
- Identified patients with at least one event of doctor-shopping for OxyContin®
- Classified patients with doctor-shopping events according to prior use of opioids (that is, 'new opioid user' with no opioid prescription filled in the 3-month look-back period, 'new OxyContin® user with prior opioid use' ascertained as at least one opioid prescription filled in the look-back period, or 'prior OxyContin® user' with at least one OxyContin® prescription filled in the look-back period)
- Determined the age, gender, and mechanism of payment for patients with an event of doctor-shopping for OxyContin®

Preliminary findings

In the interim report, findings based on data from the Ohio prescription drug monitoring program were descriptive in nature, and findings based on data from IMS LRx were both analytical and descriptive in nature. The interim report did not present findings on rates of doctor-shopping individuals per prescriptions dispensed.

Analyses with data from Ohio's prescription drug monitoring program suggest that the number of individuals considered to be doctor-shopping for OxyContin® yielded very small counts of individuals. This seemed especially true as the criteria required to identify potential doctor-shopping became more stringent, that is, as the number of pharmacies and/or the number of physicians in the algorithm increased (Figure 34).

Reference ID: 3292351

Figure 34: Number of individuals doctor-shopping for OxyContin® in Ohio, according to Ohio's prescription drug monitoring program, before (1H2009-2H2010) and after (1H2011) marketing started for reformulated OxyContin®

(b) (4)

Data source: Table 37 in the interim report entitled "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"

Note: The interim report was not clear on whether the number of pharmacies and physicians enumerated in the interim report refers to an absolute number or a range of numbers (such as 3 pharmacies, rather than 3+ pharmacies).

Whether analyses performed with data from Ohio's prescription drug monitoring program used an absolute number or range of numbers of pharmacies and physicians (such as 3 pharmacies, rather than 3+ pharmacies) to define doctor-shopping for this interim report was not clear. Therefore, the Reviewer could not evaluate Purdue's finding that more stringent definitions of doctor-shopping (4+ prescribers / 4+ pharmacies) showed reductions in potential doctor-shopping after marketing started for reformulated OxyContin®, but other, less stringent definitions did not indicate reductions.

Analyses with IMS LRx data showed that the percent of patients with overlapping OxyContin® prescriptions prescribed by 2 or more prescribers and filled at 3 or more pharmacies was lower in 1H2011-2H2011 (between (b) (4) of OxyContin® patients) than in 2H2009-1H2010 (between (b) (4)) (Table 29). The reductions in the percent of OxyContin® users who are potentially doctor-shopping for OxyContin® were more pronounced among patients paying at least once by cash, younger patients, and patients who had filled OxyContin® within the three months prior to the start of each 6-month study period.

According to analyses performed with IMS LRx, the relative risk of being an individual who was doctor-shopping for OxyContin® in 2H2011 versus 1H2010 was (b) (4), 95% confidence interval (CI) (b) (4)]. Purdue did not describe the methods used to generate this relative risk and 95% CI, so the Reviewer could not evaluate this finding.

Reference ID: 3292351

Table 29: Percent of patients who filled OxyContin® prescriptions and could be considered doctor-shopping for OxyContin®, according to the algorithm for filling overlapping prescriptions prescribed by 2 or more doctors and 3 or more pharmacies, before (2H2009-1H2010) and after (1H2011-2H2011) marketing started for reformulated OxyContin®

(b) (4)

[redacted]

Data source: Table 42 in the interim report entitled "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"

Division of Epidemiology II Reviewer comments

In summary, it appears that there was a decrease in doctor-shopping – as defined by this investigation – after marketing started for reformulated OxyContin®, compared to before marketing started. However, it is unknown whether the definition of doctor-shopping used in this investigation accurately and reliably identifies doctor-shopping. That is, no studies (such as concurrent or predictive validation studies) have been conducted to determine whether the individuals identified by this investigation's algorithms are truly doctor-shopping and/or have clinical outcomes of interest, such as addiction, overdose, or death.

Reference ID: 3292351

3.2.5 Chat Rooms Investigation

Data source/data collection

This qualitative investigation used the web-grabber technology of Web Informed Services, a component of the NAVIPPRO™ System, to prospectively collect data on internet forum posts[h] from August 2010 to April 2012, and retrospectively collect data on posts from August 2008 to August 2010.

Overview of methods/analyses

The Chat Rooms Investigation aims to characterize and assess trends in the amount and nature of online discussions regarding reformulated OxyContin® and the comparator opioids, Vicodin® and Dilaudid®, before and after marketing started for reformulated OxyContin®.

The interim report did not provide baseline data for the period of August 2008 to August 2010.

Posts from selected internet forum websites related to opioid abuse are analyzed using a standardized methodology. Specifically, trained coders use a predefined coding manual to categorize posts associated with each opioid by topic category (route of administration, extraction, procurement, negative consequences, and general) and by type of endorsement for drug abuse of the opioid (endorsing, discouraging, mixed, unclear, and not abuse-related).

This investigation examined the product-specific proportion of posts for each topic category and product-specific proportion of endorsement.

Preliminary findings

Between February 2011 and January 2012, at least 50% of the topic categories for posts related to reformulated OxyContin® were general in nature (Figure 35). The proportion of posts for the topic categories of routes of administration and extraction methods were statistically significantly lower in October 2011 through January 2012 than in February 2011 through May 2011. However, the proportion of posts on the other topic categories (that is, procurement and negative consequences) remained constant.

The protocol and the interim reports did not describe formal statistical analyses used to characterize and assess trends in the amount and nature of online discussion.

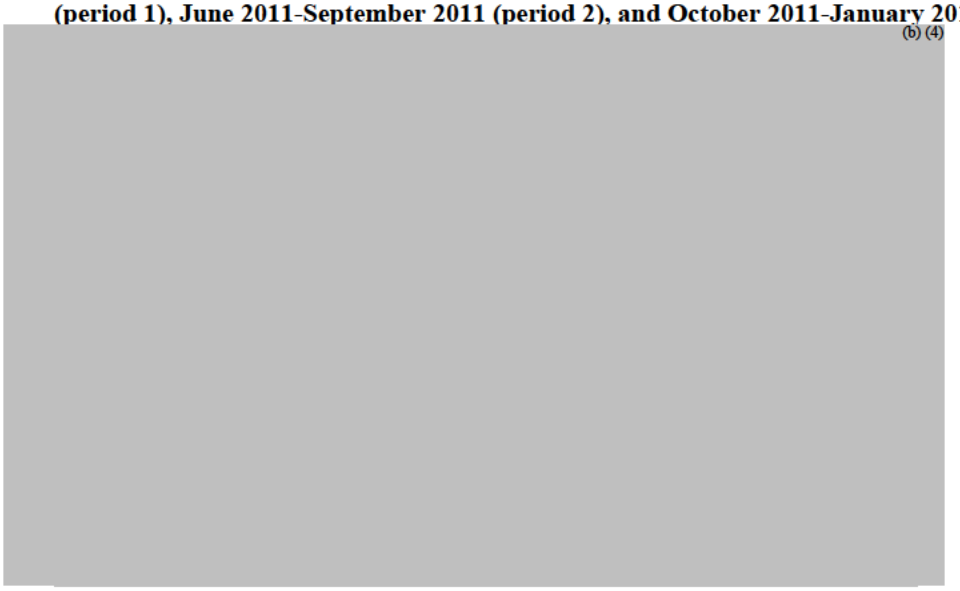
---

[h] Posts – according to this investigation's protocol, "A single message entered by one user [of the internet forum]."

Reference ID: 3292351

Figure 35: Proportion of posts associated with reformulated OxyContin®, according to Web Informed Services of the NAVIPPRO™ System, by topic category, for February 2011-May 2011 (period 1), June 2011-September 2011 (period 2), and October 2011-January 2012 (period 3)

(b) (4)



Data source: Figure 37 in the interim report entitled "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"

The proportion and pattern of endorsing, discouraging, and non-abuse related posts were unchanged for reformulated OxyContin® and the comparators between the period June 2010 – September 2011 and the period November 2010 – January 2011. However, while the proportion of mixed posts associated with reformulated OxyContin® remained constant between the two periods, the proportion of mixed posts associated with the comparators increased in 2011. The proportion of unclear posts increased for both reformulated OxyContin® and the comparators, but the pattern remained the same, with reformulated OxyContin® having the highest proportion of posts with unclear endorsement, followed by Vicodin® and Dilaudid®, respectively.

Division of Epidemiology II Reviewer comments

For multiple reasons, the proper interpretation of these results is unclear:

- Measurements from the baseline period of August 2008 – August 2010 were not provided.
- The selection of different comparators from the other investigations in the postmarketing study program precludes placing these analyses in a larger context.
- The definitions for the topic categories and types of endorsement were not provided.

Particularly with regard to the definitions of the types of endorsement, the difference between "mixed" and "unclear" discussion categories is not clear. Since a majority of posts are consistently one of these two categories, this lack of clarity could have a large effect on the interpretability of this analysis.

Reference ID: 3292351

3.2.6 Kentucky Investigation

Data source/data collection

This investigation uses interviewer-administered survey data from a longitudinal sample of 192 survey respondents in Perry County, which is located in eastern Kentucky. All survey respondents reported abusing the original OxyContin® formulation before marketing of reformulated OxyContin®. The survey collected data on each respondent's history of substance use/abuse, including procurement source, preparation, route of administration, and days of abuse via specific routes of administration in the past 30 days (frequency of abuse). In addition, the survey collected data on demographics, employment, medical history, and psychiatric history.

According to the interim report, this investigation will reassess abuse among the survey respondents with a follow-up survey conducted six months after initial assessment.

Overview of methods/analyses

In general, the Kentucky Investigation, a cross-sectional study with a qualitative component, aims to determine the extent to which drug use patterns change following introduction of reformulated OxyContin® in Appalachian Perry County, Kentucky. Specifically, this investigation aims to

- conduct qualitative interviews among a subset of participants to further understand the impact of the reformulation on drug use patterns
- identify methods of preparation and routes of administration for pharmaceutical and illegal opioids
- identify changes in drug use patterns after marketing started for reformulated OxyContin®

This investigation's measure of drug abuse is percent of survey respondents who reported abusing specific drugs. Survey respondents were asked about their drug use during the past 30 days prior to the interview, as well as drug use during the month of August 2010.

Survey respondents were asked whether they used any of the following substances to 'get high':

- OxyContin®, including original OxyContin® and reformulated OxyContin®
- Other oxycodone, including immediate-release (IR) oxycodone
- Alcohol
- Heroin
- Methadone
- Hydrocodone
- Hydromorphone
- Fentanyl
- Benzodiazepines
- Cocaine
- Crack cocaine
- Methamphetamine

Reference ID: 3292351

- Marijuana

For the purposes of this review, results for original OxyContin®, reformulated OxyContin®, and IR oxycodone are given more attention since the interim report also gave these opioids more attention in this investigation.

Recruitment began after marketing started for reformulated OxyContin®, and the surveys were administered between December 2010 and September 2011.

The study period after marketing started for reformulated OxyContin® was December 2010 – September 2011, and the study period before marketing started was August 2010.

Preliminary findings

The percent of respondents reporting reformulated OxyContin® abuse after marketing started for reformulated OxyContin® was lower than the percent of respondents reporting abuse of original OxyContin® before marketing started for reformulated OxyContin®. Abuse of reformulated OxyContin® was mainly limited to oral routes of administration, with (b) (4) of survey respondents reporting swallowing (up from (b) (4) of survey respondents reporting abuse of the original OxyContin® formulation during August 2010), (b) (4) of survey respondents reporting chewing (up from (b) (4) of survey respondents reporting snorting (down from (b) (4), and (b) (4) of survey respondents reporting injection (down from (b) (4)).

In comparison, IR oxycodone abuse increased for most routes of administration. Specifically, the percentage of survey respondents reporting snorting and injecting IR oxycodone increased from (b) (4) and (b) (4) respectively. Oral abuse of IR oxycodone remained stable at around (b) (4) of survey respondents.

Respondents reported abusing reformulated OxyContin® less frequently than abuse of original OxyContin® in August 2010 (Table 30). This was true for both oral and non-oral routes of administration.

In comparison, among survey respondents who reported IR oxycodone abuse, the average frequency of IR oxycodone abuse via non-oral routes of administration was similar between the study periods of August 2010 and December 2010-September 2011. However, as stated previously, the number of survey respondents who reported IR oxycodone abuse increased between August 2010 and December 2010-September 2011.

Reference ID: 3292351

Table 30: Number (n) of respondents and their average number of days of product-specific abuse in the past 30 days, according to 189 survey respondents in Perry County, Kentucky, for the study periods before (August 2010) and after (December 2010 – September 2011) the marketing started for

(b) (4)

[redacted]

Data source: Table 55 in the interim report entitled "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"

Division of Epidemiology II Reviewer comments

Reviewer noted that the interim findings should be interpreted as descriptive in nature. The interim report presented point estimates with respective confidence intervals to describe the proportion of the study sample that abused OxyContin® (and comparator opioids). However, the sampling strategy and the incorrect calculations of the confidence intervals (for example, lower bounds of proportions being less than 0%) preclude interpretability of the confidence intervals presented.

These findings are anecdotal because they are based on a very small, geographically restricted sample obtained from convenience sampling, specifically community outreach and "snowball sampling."[i] As a result, findings from this investigation are not nationally generalizable.

[i] Snowball sampling is a non-probability sampling technique where existing study subjects recruit future subjects from among their acquaintances. It is used when studying a population that is difficult to reach (14; 15).

Reference ID: 3292351

3.2.7 IMS Xponent Investigation

Data source/data collection

This investigation used data collected by IMS Xponent on outpatient prescriptions dispensed in the U.S. IMS Xponent's prescription data covers approximately (b) (4) of prescriptions dispensed in the U.S., and the remainder of the prescriptions is projected.

Overview of methods/analyses

The IMS Xponent Investigation, a drug utilization study, aims to:

- assess changes in opioid prescribing among all prescribers, prescribers identified by the Abuse and Diversion Detection (ADD) program, and non-ADD prescribers, before and after marketing started for reformulated OxyContin®
- estimate changes in the prescribing of higher versus lower strengths of OxyContin®, before and after marketing started for reformulated OxyContin®
- estimate trends in the prescribing of other opioids before and after marketing started for reformulated OxyContin®
- estimate the extent of reductions in OxyContin® prescribing due to ADD prescribers
- estimate changes in the number of OxyContin® prescriptions paid for by cash, before and after marketing started for reformulated OxyContin®

The Reviewer noted that this investigation does not assess actual opioid abuse, or route-specific abuse.

The interim report for this investigation did not change since the December 2011 interim report submission.

The study period before marketing started for reformulated OxyContin® was from August 2009 through July 2010. After marketing started for reformulated OxyContin®, there were two periods: a transition period when both the original OxyContin® formulation and reformulated OxyContin® were on the market, and a post-transition study period which ended in July 2011. The end of the transition period and the beginning of the post-transition study period were not defined.

For the purposes of this investigation, prescriptions were prescribed by three groupings of prescribers:

- all prescribers
- Abuse and Diversion Detection (ADD) program prescribers
- non-ADD prescribers

Purdue has determined that it should not promote its products – including OxyContin® - to ADD program prescribers. Purdue personnel identify ADD prescribers by observing or learning about the prescribers' (prescribing) practices that are indicative of abuse and diversion.

To be eligible for this investigation, both the ADD prescribers and the non-ADD prescribers had to have a monthly average of 5+ prescriptions for OxyContin® from January 2010 – July 2010, and no more than two calendar months with no prescriptions for OxyContin® from January 2010 – July 2010.

Reference ID: 3292351

For descriptive purposes, the interim report presented prescribing data for the following prescription opioids:

- Extended-release (ER) hydromorphone
- ER morphine
- ER oxymorphone
- Generic ER oxycodone
- Immediate-release (IR) hydromorphone
- Single-entity (SE) IR oxycodone
- Methadone

The interim report's findings for this investigation were descriptive in nature as no statistical tests were applied to the IMS Xponent data.

Preliminary findings

The main findings are that a slight decline in the monthly average number of OxyContin® prescriptions dispensed was observed nationwide after marketing started for reformulated OxyContin® (Figure 36a, Figure 36b, and Figure 36c). Specifically, the monthly average number of OxyContin® prescriptions dispensed for all prescribers was (b) (4) lower after marketing started for reformulated OxyContin®, from (b) (4) prescriptions per month before marketing started to (b) (4) prescriptions per month after the transition period. The greatest declines were among OxyContin® prescriptions prescribed by ADD prescribers ((b) (4), from (b) (4) prescriptions per month before marketing of reformulated OxyContin® started, to (b) (4) prescriptions per month after the transition period). In comparison, OxyContin® prescriptions prescribed by comparator prescribers fell (b) (4) from (b) (4) prescriptions per month to (b) (4) prescriptions per month.

Reference ID: 3292351

Figure 36a: Number of outpatient prescriptions dispensed per month and prescribed by all U.S. prescribers

(b) (4)

Figure 36b: of outpatient prescriptions dispensed per month and prescribed by prescribers‡ identified by Purdue's Abuse and Diversion Detection program

(b) (4)

‡ Prescribers had to have a monthly average of 5+ prescriptions for OxyContin® from January 2010 – July 2010, and no more than two calendar months with no prescriptions for OxyContin® from January 2010 – July 2010

Reference ID: 3292351

Figure 36c: Number of outpatient prescriptions dispensed per month and prescribed by prescribers‡ who were not identified by Purdue's Abuse and Diversion Detection program

(b) (4)

Data source: Figures 42-44 in the interim report entitled "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"

‡ Prescribers had to have a monthly average of 5+ prescriptions for OxyContin® from January 2010 – July 2010, and no more than two calendar months with no prescriptions for OxyContin® from January 2010 – July 2010

The average number of OxyContin® prescriptions prescribed by all prescribers fell the most for 40 mg strengths (- (b) (4) from (b) (4) prescriptions per month before marketing started for reformulated OxyContin® to (b) (4) prescriptions per month after the transition period), and 80 mg strengths (- (b) (4) from (b) (4) prescriptions per month to (b) (4) prescriptions per month). OxyContin® prescriptions paid for with cash dropped (b) (4)

The Reviewer noted that most prescriptions dispensed for OxyContin® were for reformulated OxyContin® during the study period after marketing started for reformulated OxyContin® (Figure 40a and b). Therefore, although no IMS Xponent data were stratified by formulation, the changes in OxyContin® dosage strengths dispensed and cash payments paid reflect original OxyContin® during the study period before marketing started for reformulated OxyContin®, and reformulated OxyContin® thereafter.

Division of Epidemiology II Reviewer comments

These findings may reflect, among other things, a reduction in the demand for OxyContin® for abuse or misuse. Exactly how changes in prescribing patterns correspond to changes in behavioral (such as diversion) or clinical outcomes (such as addiction and death) is unclear. In particular, as discussed further in Section 4, the risk evaluation and mitigation strategy for OxyContin® may have influencing prescribing patterns for OxyContin®, reducing the overall prescriptions dispensed with OxyContin®.

Reference ID: 3292351

3.2.8 International Drug Safety Database (ARGUS) Investigation

Data source/data collection

This investigation uses data from the International Drug Safety Database (ARGUS), a spontaneous adverse event reporting system maintained by Purdue. Purdue Pharma's Drug Safety and Pharmacovigilance Department prospectively collects adverse event reports for both the original OxyContin® formulation and reformulated OxyContin®.

Overview of methods/analyses

The International Drug Safety Database (ARGUS) Investigation aims to assess changes in the number of adverse event reports that were reported to Purdue, coded as being at least one of four case types (drug abuse, intentional drug misuse, overdose, and medication errors), and associated with the original OxyContin® formulation or reformulated OxyContin® before and after marketing started for reformulated OxyContin®.

Because Purdue prospectively collects adverse event reports for both the OxyContin® formulations, this investigation's design is a prospective case-series. The inclusion criteria for case reports were the following:

- Cases originating in the U.S. involving the original OxyContin® from January 2010 through December 2010
- Cases originating in the U.S. involving reformulated OxyContin® from January 2011 through December 2011
- Cases originating in the U.S. involving all controlled-release formulations of oxycodone from February 15, 2009 through January 31, 2012
- Cases related to drug abuse, intentional misuse, medication error/maladministration, and overdose, according to preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0 (see Appendix H)
- Cases related to tampering according to MedDRA preferred terms, specifically, chew, crush, grind, cut, split, smoke, dissolve, break, snort, or inject

Cases having the following characteristics were excluded:

- Cases lacking one or more core elements (that is, a patient, a reporter, a suspect product, or an adverse event)
- Legal cases originating from report sources related to U.S. litigation (that is, cases that, according to Purdue, are not typically reported by healthcare professionals and contain little specific information with which to assess event causality)
- Cases with adverse event occurring outside the U.S.

The interim report defined two study periods with respect to when marketing started for reformulated OxyContin®. Specifically, the study period before marketing started was from January 2010 through December 2010, and the study period after marketing started was from January 2011 through December 2011.

All findings presented for the ARGUS Investigation were descriptive in nature in the July 2012 interim report.

Reference ID: 3292351

Preliminary findings

ARGUS had 1,272 unique case reports involving original OxyContin® before marketing started for reformulated Oxycontin® and 819 unique case reports involving reformulated OxyContin®, both associated with drug abuse, intentional drug misuse, medication error/maladministration, and/or overdose (Table 31).

When stratified by case type, the number of cases associated with drug abuse, overdose, and medication error/maladministration, and was consistently lower for reformulated OxyContin® than for original OxyContin®: 894 drug abuse cases associated with original OxyContin® vs. 499 drug abuse cases associated with reformulated Oxycontin®; 240 vs. 120 overdose cases, and 155 vs. 131 medication error/maladministration cases, respectively. The number of intentional drug misuse cases involving original OxyContin® before marketing started for reformulated OxyContin® (146 cases) was similar to the number of intentional drug misuse cases for reformulated OxyContin® (150 cases)

Table 31: Number of unique case reports reported to Purdue's International Drug Safety Database (ARGUS), before (January 2010-December 2010) and after (January 2011-December 2011) marketing started for reformulated OxyContin®, by OxyContin® formulation and case type

Case Type	Original Oxycontin® formulation (January 2010-December 2010)	Reformulated Oxycontin® (January 2011-December 2011	Relative Percent Difference
Total‡	1,272	819	-36%
Drug abuse	894	499	-44%
Overdose	240	120	-50%
Medication error / maladministration	155	131	-16%
Intentional drug misuse	146	150	+3%

Data source: Tables 59-63 in the interim report entitled "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"

‡ For each case report, Purdue Pharma Drug Safety and Pharmacovigilance Department can code multiple case types, such as cases involving both drug abuse and overdoses. Therefore, the sum of the number of unique case reports for the four case types is greater than the total number of unique case types.

An abstract submitted to the Sep 2012 PAINWeek conference contained updated information for fatal OxyContin® cases. Between August 2009 and March 2012, ARGUS had 753 case reports, of which 409 (56%) did not contain information on the dates of death. Therefore, although analyses on the remaining 344 fatal case reports found the number of fatal cases declined after the marketing started for reformulated OxyContin®, it is unclear if these reductions are biased by missing data.

Division of Epidemiology II Reviewer comments

Purdue states that the postmarketing data suggest that the reformulation may be having the desired effect of reducing misuse and abuse of OxyContin®. However, since these data represent passive surveillance, these changes may be the result of other factors that affect reporting or

Reference ID: 3292351

interpretation of case reports, such as underreporting, missing information, inability to assign causality, recall bias, and confounding (46).

Reference ID: 3292351

4 DISCUSSION

Question for discussion: What evidence in Purdue's postmarketing study program best demonstrates or suggests that reformulated OxyContin® has abuse deterrent properties?

Among all the investigations in Purdue's postmarketing study program, the NAVIPPRO™ Investigation contains the most suggestive evidence that reformulating OxyContin® has deterred it from abuse, particularly via non-oral routes of administration. For multiple reasons, however, these preliminary findings from the NAVIPPRO™ Study do not provide definitive evidence of abuse-deterrence.

The NAVIPPRO™ Investigation's interim analyses consistently found that adults entering substance abuse treatment reported abuse of reformulated OxyContin® less than abuse of original OxyContin®. Compared to abuse of original OxyContin® before marketing started for reformulated OxyContin®, abuse of reformulated OxyContin® was statistically significantly lower in terms of:

- overall (that is, not route-specific) prevalence of abuse
- prevalence of abuse via any oral route of administration
- prevalence of abuse via non-oral routes of administration (all, injection, smoking, and snorting)
- percent of adults abusing OxyContin® via non-oral routes of administration
- number of days of abuse in the past 30 days

Additionally, the above findings were accompanied by increases in ER oxymorphone abuse for each of the measures above. However, ER morphine abuse did not appreciably change.

Purdue concluded that this investigation found substantially lower abuse rates for reformulated OxyContin® than for historical abuse of original OxyContin®.

However, it is unknown if Purdue's conclusion of the NAVIPPRO™ Investigation results will be robust after this investigation does the following:

- adjusts for availability of each ER oxycodone formulation, which is important given that generic ER oxycodone, original OxyContin®, and reformulated OxyContin® were all abused after marketing started for reformulated OxyContin®
- explores changes in oral routes of administration that require tampering (for example, chewing), before <u>and</u> after marketing started for reformulated OxyContin®
- analyzes data from a stable selection of substance abuse treatment centers
- extends the length of the investigation

Most importantly, the persistence in original OxyContin® abuse observed in the NAVIPPRO™ Investigation – and the RADARS® SPCP Investigation – confounds the prevalence of reformulated OxyContin® abuse[j]. That is, the persistence in original OxyContin® abuse makes it

[j] Note: Abuse of other ER oxycodone, which includes generic ER oxycodone and OxyContin® from Mexico and Canada, was also prevalent after marketing started for reformulated OxyContin®; however, the Reviewer could not conclude that abuse of these versions of ER oxycodone were 'persisting' since the Reviewer did not have data on the prevalence of abuse for these opioids throughout time.

Reference ID: 3292351

difficult to assess how prevalent reformulated OxyContin® abuse may be when original OxyContin® is not being abused.

It is particularly notable that the available data presented for the NAVIPPRO™ Investigation – or the RADARS® SPCP Investigation – do not adequately explain the persistence of original OxyContin® abuse. All explanations for this persistence are speculative.

One possible explanation is misclassification of abuse of other substances - that is, not original OxyContin® - as abuse of original OxyContin®. In the Reviewer's opinion, adults entering substance abuse treatment are equally likely to misclassify abuse of other substances as abuse of either formulation of OxyContin®. Therefore, if misclassification of abuse of other substances existed, then the misclassification would be non-differential with respect to OxyContin® formulation. *Note: Only* (b) (4) *of adults entering substance abuse treatment centers participating in the NAVIPPRO™ surveillance system reported abusing a 'fake' product. This demonstrates specificity, although not with regards to OxyContin®.*

However, misclassification between OxyContin® formulations is more probable since the main visual difference between OxyContin® formulations is their imprint (for example, "OC" or "OP," see Figure 1).

Misclassification may be present between the OxyContin® formulations, but the route of administration profiles of abuse suggest that the persistence in original OxyContin® abuse cannot be explained only by misclassification. Specifically, the routes of administration profile for original OxyContin® abuse seemed to shift away from non-oral to oral routes of administration, suggesting that misclassification of reformulated OxyContin® as original OxyContin® may exist. However, in 3Q2012, the routes of administration profile of abuse was still seemingly different between original OxyContin® and reformulated OxyContin®, albeit less different than in 3Q2010 when reformulated OxyContin® was first marketed.

An alternative, but no less speculative, explanation of the persisting original OxyContin® abuse is a differential preference for abusing the remaining original OxyContin® supply, even after distribution of original OxyContin® ceased. Preference for abuse of original OxyContin® could imply that, compared to original OxyContin®, reformulated OxyContin® has abuse deterrent properties when both formulations are available via legal and illegal channels of distribution. However, individuals who abuse original OxyContin® may eventually shift abuse to reformulated OxyContin® after they exhaust all their supply of original OxyContin®. Therefore, the abuse deterrent properties of reformulated OxyContin® could be short lived.

Another speculative explanation for the persistence of original OxyContin® abuse is a substantial lag time between the dispensing and abuse of original OxyContin®. While the average lag time is unknown, the existence of a lag time is reasonable.

Lastly, diversion of original OxyContin® from outside the U.S., or illegal manufacturing of counterfeit original OxyContin®, could be other explanations of the persistence of original OxyContin® abuse. In the Reviewer's opinion, this explanation is reasonable given that the decreases in original OxyContin® prescriptions dispensed and the presence of reformulated OxyContin® may make these procurement sources more attractive to those who abuse original OxyContin®. However, it is unlikely that an accurate measure of diverted or counterfeit original OxyContin® exists, so this explanation is still speculative.

Reference ID: 3292351

Question for discussion: What are the overarching limitations in Purdue's postmarketing study program?

Each investigation in Purdue's postmarketing study program could be stronger if it was not missing one or more of the following characteristics allowing for a better assessment of reformulated OxyContin® abuse:

- stratification of abuse by routes of administration
- stratification of ER oxycodone abuse by formulation
- direct assessment of abuse or misuse
- examination of clinical outcomes, specifically, addiction, overdose, poisoning, and death
- focus on an at-risk population
- accounting for availability of each ER oxycodone formulation for abuse
- addressing the effect of the OxyContin® risk evaluation and mitigation strategy (REMS), which was instituted when marketing started for reformulated OxyContin®, on abuse and misuse of OxyContin®
- assessment of changes in level and trend

It is important to note that, to date, Purdue has not provided any robust data on the clinical outcomes of overdose, poisoning, and death, and the clinical outcome of addiction has not been formally assessed.

Note: The ARGUS Investigation did provide data on OxyContin®-related mortality, but the large percent of ARGUS' spontaneous reports with missing dates of death preclude this investigation from providing support for an effect of the reformulation of OxyContin® on OxyContin®-related deaths.

Of all the investigations in Purdue's postmarketing study program, the NAVIPPRO™ Study has the strongest design because it addresses most of these characteristics (Table 32).

Other investigations have some of these characteristics. However, Purdue's postmarketing study program depends on a 'mosaic' approach to address the postmarketing requirement, including investigations that aim to provide a strength (or different perspective) that complements the weaknesses of the other investigations.

Reference ID: 3292351

Table 32: Summary of characteristics enabling a strong assessment of drug abuse, by investigation in Purdue's postmarketing study program

Investigation		Examines addiction, overdose, poisoning, or death	Stratifies abuse by routes of administration?	Stratifies ER oxycodone abuse by formulation?	Directly assesses abuse and misuse?	Focuses on an at-risk population?	Accounts for availability of ER oxycodone for abuse?	Assesses changes in level and trend?
NAVIPPRO		Addiction (implied)	Yes	Yes	As reported abuse in past 30 days	Yes	Dispensed prescriptions	Level only Planned: Trend
RADARS System Poison Center Program		Death	Planned	Possibly	As abuse and misuse exposures	No	Recipients dispensed prescriptions	Level only Planned: Trend
National Poison Data System		No	No	No	As abuse and misuse exposures	No	Dispensed prescriptions	Level only
Kaiser Permanente Health System		No	Planned	Yes	No	No	Planned	Planned: Both
National Surveys		No	Planned for RADARS® College Survey	No	As non-medical use	No	No	Level only
RADARS® System Drug Diversion Program	**Diversion Cases**	No	No	No	No	Yes	Dispensed prescriptions	Level only
	Street Prices	No	No	Yes	No	Yes	No	Level only
Doctor Shopping		No	No	No	No	No	Dispensed prescriptions	Level only
RADARS® System Chat Rooms		Yes	Yes	Yes	As reported abuse	Yes	No	Level only
Kentucky		Addiction (implied)	Yes	Yes	As reported abuse	Yes	No	Neither
IMS Xponent		No	No	Yes	No	No	No	Level only
International Drug Safety Database (ARGUS)		Overdose and death	Yes	Yes	As reported abuse and misuse	No	No	Level

Reference ID: 3292351

Examination of clinical outcomes, specifically, addiction, overdose, poisoning, and death

Assessments of overdoses and poisonings as well as mortality, all of which are an integral part of the postmarketing requirement, were missing from the three formal studies in this interim report.

Overall, Purdue's postmarketing study program needs more information on changes in these clinical outcomes. The RADARS® SPCP Investigation is the only formal study designed to explore death in terms of mortality rate and case fatality rate; however, no data on these outcomes were provided in the interim report. NPDS could also explore these outcomes, but the sponsor has not proposed to do so. *(Note: Although poison control data are likely to undercapture death, assessing changes in mortality rate and case fatality rate would be informative and supplement assessments of changes in intentional abuse exposures).* It is unknown if the NAVIPPRO™ Investigation could explore severity and duration of addiction. None of the three formal studies could be re-designed to study prevalence or severity of overdoses and poisonings.

Stratification of abuse by routes of administration and formulation

The three formal studies of abuse had many findings on overall abuse, but did not have many findings addressing the direct effect that the reformulation of OxyContin® is hypothesized to have on non-oral abuse of OxyContin®.

Purdue also planned to assess the prevalence of route-specific abuse with the RADARS® SPCP Investigation. However, the interim report did not have any findings on route-specific abuse, and the protocol for this investigation did not differentiate between OxyContin® formulations. Because the interim report for this investigation presented data on overall abuse per formulation, this investigation – and possibly the NPDS Investigation – could conceivably assess route-and formulation-specific abuse. Five other investigations in Purdue's postmarketing study program also examine abuse and misuse via specific routes of administration. However, two investigations – the Kaiser Permanente Health System Investigation and the National Surveys Investigation - do not have interim findings on routes of administration of abuse. The other three investigations – Chat Rooms Investigation, Kentucky Investigation, and the ARGUS Investigation – lack generalizability.

To compare abuse (such as prevalence of abuse) of reformulated OxyContin® to original OxyContin®, investigations must determine the formulation of ER oxycodone being abused. These formulations included the original ER oxycodone formulation – both brand and generic – and the reformulated ER oxycodone formulation (that is, reformulated OxyContin®). However, this is a difficult task because all brand and generic formulations were available for abuse after marketing started for reformulated OxyContin®. Only the ASI-MV® survey in the NAVIPPRO™ Investigation aims to ensure that study subjects accurately identify the formulation of ER oxycodone that they abused.

Direct assessment of abuse or misuse

Directly assessing abuse and misuse behaviors (such as reported drug abuse) is more informative than assessing surrogate measures of abuse and misuse behaviors. Surrogate measures assessed in Purdue's postmarketing study program include:

- drug diversion cases
- street prices
- doctor-shopping
- chat room endorsement

Reference ID: 3292351

- surveys and interviews
- prescribing behavior

These surrogate measures require additional validation efforts that adequately quantify how well they predict actual abuse and misuse and the clinical consequences of abuse and misuse.

Focus on an at-risk population

Studying an at-risk population increases statistical power, enabling an investigation to observe larger reductions in abuse than when studying a more general population. As a case in point, both the NAVIPPRO™ Investigation and the National Surveys Investigation assess changes in the prevalence of OxyContin® abuse. However, the National Surveys Investigation may not be as likely as the NAVIPPRO™ Investigation to observe large reductions in the prevalence of OxyContin® abuse because, unlike the NAVIPPRO™ Investigation, the National Surveys Investigation does not focus specifically on an at-risk population. The National Surveys Investigation simultaneously assesses individuals at-risk and not at-risk of OxyContin® abuse within the general population. However, the individuals not at-risk may add considerable noise to the investigation, therefore, reducing the statistical power to observe reductions in abuse that may occur among individuals at-risk. This limitation does not apply to the NAVIPPRO™ Investigation, where the population focuses on an at-risk individuals entering substance abuse treatment.

Furthermore, individuals in the general population and who have less experience with prescription opioid abuse have a different substance abuse and opioid tolerance profile than individuals with more experience with prescription opioid abuse. In particular, those with more experience with prescription opioid abuse are more likely to abuse prescription opioids via non-oral routes of administration, the routes which the reformulation of OxyContin® is intended to affect.

Accounting for availability of OxyContin® for abuse

Unlike the other two formal studies of abuse, the NAVIPPRO™ Investigation's findings did not appropriately account for the availability of OxyContin® for abuse. The RADARS® SPCP Study and the NPDS Study adjusted for unique recipients dispensed OxyContin® and prescriptions dispensed, respectively.

The Reviewer recommends that the three formal studies of abuse assess changes in the extended unit-adjusted rates of abuse before and after marketing started for reformulated OxyContin®. In the case of OxyContin®, extended units are OxyContin® tablets. As an example, the calculation of extended unit-adjusted rates of reformulated OxyContin® abuse is:

Equation 9

$$\text{extended-unit adjusted rate of reformulated OxyContin® abuse} = \frac{\text{\# individuals who abused reformulated Oxycontin®}}{\text{\# reformulated Oxycontin® tablets dispensed}}$$

The rates calculated in Equation 3, Equation 8, and Equation 9 has three different interpretations. The extended unit-adjusted rate of OxyContin® abuse implies that every tablet dispensed for OxyContin® represents an opportunity for OxyContin® abuse. Similarly, the prescription-adjusted rate of OxyContin® abuse, which the NPDS Investigation examined and the NAVIPPRO™ Investigation plans to examine, implies that every prescription dispensed for OxyContin® represents an opportunity for OxyContin® abuse. Lastly, the recipient-adjusted

Reference ID: 3292351

rate, a rate which the RADARS® SPCP Investigation examined, implies that every recipient of OxyContin® has a probability of abusing OxyContin®.

The numerator and the denominators for each of these rates – especially for recipient-adjusted rates – differ by catchment area. The numerators all reflect a measure of OxyContin® abuse, including abuse of diverted OxyContin®. However, both the extended unit- and prescription-adjusted rates of abuse also do not account for extended units or prescriptions originating – including diverted prescriptions – from outside the U.S. or for counterfeit tablets. Similarly, the recipient-adjusted rate does not account for diverted OxyContin® tablets or prescriptions.

In the Reviewer's opinion, the recipient-adjusted rate uses a denominator that, compared to the other rates, grossly underestimates the catchment area represented in the numerator, particularly since prescription pain killers are often procured from others' prescriptions[k].

Because the extended unit-adjusted rate allows for assessment of OxyContin® abuse at a more granular level than the prescription-adjusted rate, evaluation of changes in extended unit-adjusted rates of abuse will yield more accurate results than evaluation of changes in prescription-adjusted rates of abuse.

The Reviewer acknowledges that, to some extent, there is a lag from when a prescription is dispensed to when it could be abused. Currently, the investigations that account for a measure of the availability of OxyContin® for abuse do not assess possible lag; that is, they assume that opioids are abused in the same time period (such as quarter-year) as they are dispensed. These investigations also assume that for each unit increase in the measures of the availability of OxyContin® for abuse, there is a linear increase in the measures of drug abuse. No investigation in Purdue's postmarketing study program currently addresses these assumptions.

Addressing the effect of the OxyContin® risk evaluation and mitigation strategy (REMS), which was instituted when marketing started for reformulated OxyContin®, on abuse and misuse of OxyContin®

Reductions in various measures of abuse may be confounded by the concomitant implementation of a Risk Evaluation and Mitigation Strategy (REMS), which was specific to reformulated OxyContin® (48). This REMS program targeted two risks:

- Potential for abuse, misuse, overdose, and addiction
- Use of doses greater than 40 mg of OxyContin® in non-opioid tolerant patients

The program consisted of a communication plan (Medication Guide and Dear Healthcare Professional letters) and healthcare provider training not linked to prescribing or dispensing. The REMS assessment plan included evaluations of patients' and healthcare providers' understanding of risks associated with OxyContin®, and other programmatic evaluations not directly aimed at changing patient or prescriber behavior.

A REMS assessment found reductions in inappropriate prescribing, as is indicated by reductions in 80 mg OxyContin® doses among both opioid-naïve and opioid-tolerant patients after

---

[k] According to the National Survey on Drug Use and Health, only (b) (4) of those reporting nonmedical use of prescription pain killers reported obtaining their most recent supply of prescription pain reliever from a legitimate prescription prescribed to them (47). Another (b) (4) that reported nonmedical use of prescription pain killers reported obtaining their most recent supply of prescription pain reliever from someone else.

Reference ID: 3292351

marketing started for reformulated OxyContin® (49). Therefore, the REMS program could confound this postmarketing study program by affecting:

- the overall abuse risk among patients prescribed OxyContin®
- availability of high doses of OxyContin®

However, these potentially confounding factors may or may not affect abuse via routes of administration that require tampering. On one hand, the combination of limiting high doses of OxyContin® plus lower abuse risk among patients prescribed OxyContin® may make OxyContin® generally less attractive for abuse, including abuse via non-oral routes of administration. On the other hand, while being generally less attractive for abuse may affect the prevalence of abuse via non-oral routes of administration, it may not necessarily result in changes in the route-specific patterns of abuse.

Furthermore, the OxyContin® REMS was not designed to specifically reduce diversion, so the effect of REMS on OxyContin® abuse may be limited due to extensive diversion[k].

The potential confounding introduced by the REMS cannot be remedied. Only one opioid product had REMS implemented closely in time to the introduction of ORF: Suboxone Sublingual Film with a REMS implemented in Aug 2010 (50). However, unlike OxyContin®, this opioid is used in the treatment of opioid dependence and has a restricted distribution program (specifically, a Drug Enforcement Agency requirement of prescriber certification). Therefore, Suboxone Sublingual Film is not an appropriate comparator to assess the effect of REMS on abuse. An ER/LA opioid class REMS, which included OxyContin®, was approved in July 2012, so OxyContin® may be more comparable with other opioids with regards to REMS from 3Q2012 and beyond.

Assessment of changes in level and trend

Longer follow-up and completion of the proposed analyses are needed to appropriately evaluate the effect of the new formulation of OxyContin® on abuse and misuse. From an epidemiological perspective, longer follow-up is necessary to assess if abusers will find and utilize tampering techniques that enable non-oral abuse. In addition, legal and illegal supplies of original OxyContin® and generic ER oxycodone seem to be abused long after reformulated OxyContin® was introduced and distribution ceased for these products, so a longer follow-up will likely allow confounding by the abuse of original ER oxycodone products to reduce as supplies of these products diminish. From a statistical perspective, longer follow-up will help the investigations assess both level and trend in OxyContin® abuse. Simple pre-post analyses are informative with respect to comparing changes in the level of abuse and misuse before and after marketing started for reformulated OxyContin®, but these analyses do not preclude favorable or unfavorable trends.

The Reviewer recommends a follow-up period of 3 to 5 years after marketing started for reformulated OxyContin® for completion of Purdue's postmarketing requirement.

In recommending this, the Reviewer believes that the length of follow-up:

- should balance the aim of assessing short-term reductions (if any) in OxyContin® abuse and the aim of assessing the sustainability of those reductions
- should not be prohibitively long in addressing the postmarketing requirement
- should enable an investigation to characterize the trend in OxyContin® abuse after marketing started for reformulated OxyContin®

Reference ID: 3292351

- should allow for the completion of planned analyses and assessments of clinical outcomes
- should be long enough to assess whether abuse of original OxyContin® will eventually decrease again
- was suggested, in part, by the October 2010 Anesthetic and Analgesic Drug Products Advisory Committee

In general, investigations must be sufficiently long to evaluate whether reductions in abuse observed in those investigations are real.

Within this general statement, there are two aims. The first aim is to ensure that the study length is sufficiently long enough to observe reductions in levels of abuse, and the second aim is to confirm that those short-term reductions were, indeed, real and sustained.

For the first aim, published observational studies on the opioid agonist-antagonist combination pentazocine-naloxone (brand name Talwin® NX) suggest that one to two years of follow-up may be sufficient to observe immediate reductions in abuse. In the observational study by Baum et al., prescription-adjusted rates of emergency room visits and medical examiner mentions associated with pentazocine were 70% and 71% lower, respectively, before versus after distribution of pentazocine-naloxone replaced distribution of pentazocine. The length of the study periods before and after marketing started for pentazocine-naloxone was 2.25 years and 2 years, respectively. These study periods were subdivided into quarter-year intervals. See Appendix I for more details on this study.

However, longer follow-up may be needed to assess sustainability of abuse deterrence. As an example, a Cicero et al. conducted a study on the abuse of tramadol and found that the recipient-adjusted rates of abuse did not stabilize in the first two years after marketing started for tramadol (Figure 37) (51). The study observed that abuse rates stabilized during the third to seventh year following initial marketing.

Reference ID: 3292351

Figure 37: Trends in abuse may require three or more years to attain sustainability, as suggested by a study on tramadol abuse (51)

Copyright Material

In the Reviewer's opinion, although continued surveillance of OxyContin® abuse is needed while OxyContin® is marketed, fulfillment of the postmarketing requirement should not take prohibitively long, especially since study results and their interpretation are likely to be affected by eventual changes in the market and other factors. Again, as an example, the study on tramadol abuse suggests that recipient-adjusted cases of withdrawal associated with tramadol was sharply affected by the introduction of tramadol-acetaminophen to the market (Figure 38) (51).

Figure 38: Trends in abuse may sharply change as a result of changes in the market or other factors, as suggested by the sharp increase in tramadol withdrawal cases following the introduction of tramadol-acetaminophen to the market (51)

Copyright Material

From a statistical perspective, Purdue's postmarketing study program will need more than 1.75 quarter-years worth of data (7 data points from 3Q2010 to 1Q2012) to fully characterize the trend in OxyContin® abuse after marketing started for reformulated OxyContin®. The number of data points needed to assess trend may vary among investigations and will depend on:

- the variability of the study measure
- possible bias in the study measure
- extent of autocorrelation among data points
- presence of possible periodical or seasonal patterns in the data

The interim findings from the NAVIPPRO™ Investigation and the RADARS® SPCP Investigation found that abuse of original OxyContin® persisted even though prescriptions dispensed with original OxyContin® decreased rapidly after marketing started for reformulated OxyContin®. Additional follow-up will enable each of these investigations to assess whether the depleting licit supply – and possibly illicit supply – of original OxyContin® will eventually yield further declines in original OxyContin® abuse. If original OxyContin® abuse does not decline further, misclassification of reformulated OxyContin® as original OxyContin® could be a likely explanation for the persistence in abuse of original OxyContin®.

Question for discussion: Did the interim findings from the supplemental investigations contribute to the formal studies in terms of demonstrating or suggesting that reformulated OxyContin® has abuse deterrent properties?

Regarding a 'mosaic' approach to addressing the postmarketing requirement for reformulated OxyContin®, the interim report was not formatted in a way that allowed the eight additional investigations to provide context and support for the findings from the three formal studies of abuse.

These eight investigations may provide additional context to the formal studies in terms of the following:

- Drug utilization and supply of OxyContin®
- Qualitative assessment of OxyContin® abuse
- Mortality

The IMS Xponent Investigation and the Doctor Shopping Investigation could provide Purdue's postmarketing study program with drug utilization data, namely quantity of prescriptions dispensed, prescribing and dispensing characteristics, and patient demographics. The illicit supply of diverted OxyContin® is unknown, and the RADARS® Drug Diversion Investigation cannot provide supply information because law enforcement diversion cases are non-random events.

The Chat Rooms Investigation could provide important qualitative data on attitudes toward and practices of overall and route-specific abuse of OxyContin®. Discussion on how drug abusers attempt to tamper with reformulated OxyContin® could generate hypotheses on possible novel tampering techniques that may lead to increases in non-oral abuse of OxyContin®. Furthermore, the Chat Rooms Investigation assesses attitudes and practices from a large number of abusers, as suggested by the (b) (4) unique authors (some of which may be duplicate people) in year 2011 alone. On the other hand, the Kentucky Investigation, which also has a qualitative component, does not provide a diversity of attitudes and practices because the study uses a geographically restrictive sample of (b) (4) drug abusers.

The Kaiser Investigation and the ARGUS Investigation, as supplemental investigations, could support findings regarding OxyContin®-related mortality. However, RADARS® SPCP Investigations and the NDPS Investigations, both which are formal studies of abuse, did not have interim findings on mortality.

Question for discussion: If the interim findings from the formal studies of abuse are accurate, then do the interim findings represent meaningful reductions in OxyContin® abuse?

To establish a context for what constitutes a meaningful reduction, the Reviewer conducted a non-systematic review of the medical literature to identify interventions – such as marketing of a proposed abuse deterrent formulation – that have been associated with reductions in opioid abuse (see Appendix I). Further details on the excluded studies are not provided because the search was not systematic.

Four studies were identified that assessed how abuse changed after marketing started for a reformulated opioid and distribution of the original opioid formulation ceased. The original opioids and their reformulated versions are:

Reference ID: 3292351

- pentazocine and pentazocine-naloxone
- buprenorphine and buprenorphine-naloxone

Similar to abuse of original OxyContin®, abuse of the original formulations of pentazocine and buprenorphine was via oral and non-oral routes of administration, particularly injection. Naloxone is an opioid antagonist that has no pharmacologic activity when ingested, but will antagonize the effects of these opioids when injected. The authors of these four studies stated that the addition of naloxone to either pentazocine or buprenorphine may be associated with the decrease in abuse of pentazocine or buprenorphine.

The study designs differed among the four studies, particularly with respect to the population studied, measures of drug abuse, and data sources used. Therefore, none of the four studies identified in this non-systematic review are directly comparable to the three formal studies of OxyContin® abuse. Appendix I summarizes the four studies the Reviewer identified.

If the findings from the three formal studies are accurate, then the decreases in OxyContin® abuse observed in these studies are within the range of decreases in abuse observed in the four studies of opioid agonist-antagonists, which may be abuse-deterrent formulations (Table 33 and Figure 39).

The results from the formal studies do not consider abuse of other ER oxycodone (such as generic ER oxycodone) and, for the NAVIPPRO™ Investigation, the persistence in original OxyContin® abuse.

That being said, the decreases in abuse observed in the three formal studies of OxyContin® abuse were generally larger than decreases in abuse observed in studies of buprenorphine abuse, but were somewhat smaller than the decreases in abuse observed in the one study of pentazocine abuse. In the three formal studies of OxyContin® abuse, the relative percent differences in the various measures of OxyContin® abuse ranged from (b) (4) Meanwhile, the relative percent differences in the various measures of buprenorphine abuse ranged from (b) (4) However, the relative percent differences in the various measures of pentazocine abuse ranged from (b) (4)

In summary, it is difficult to compare the reductions in abuse among these possibly abuse-deterrent formulations:

- The findings from the formal studies in Purdue's postmarketing study program do not provide definitive evidence of abuse-deterrence given the abuse of all ER oxycodone formulations – both brand and generic – after marketing started for reformulated OxyContin®.
- The populations, measures of drug abuse, and the data sources are different among the studies and investigations reviewed.

Reference ID: 3292351

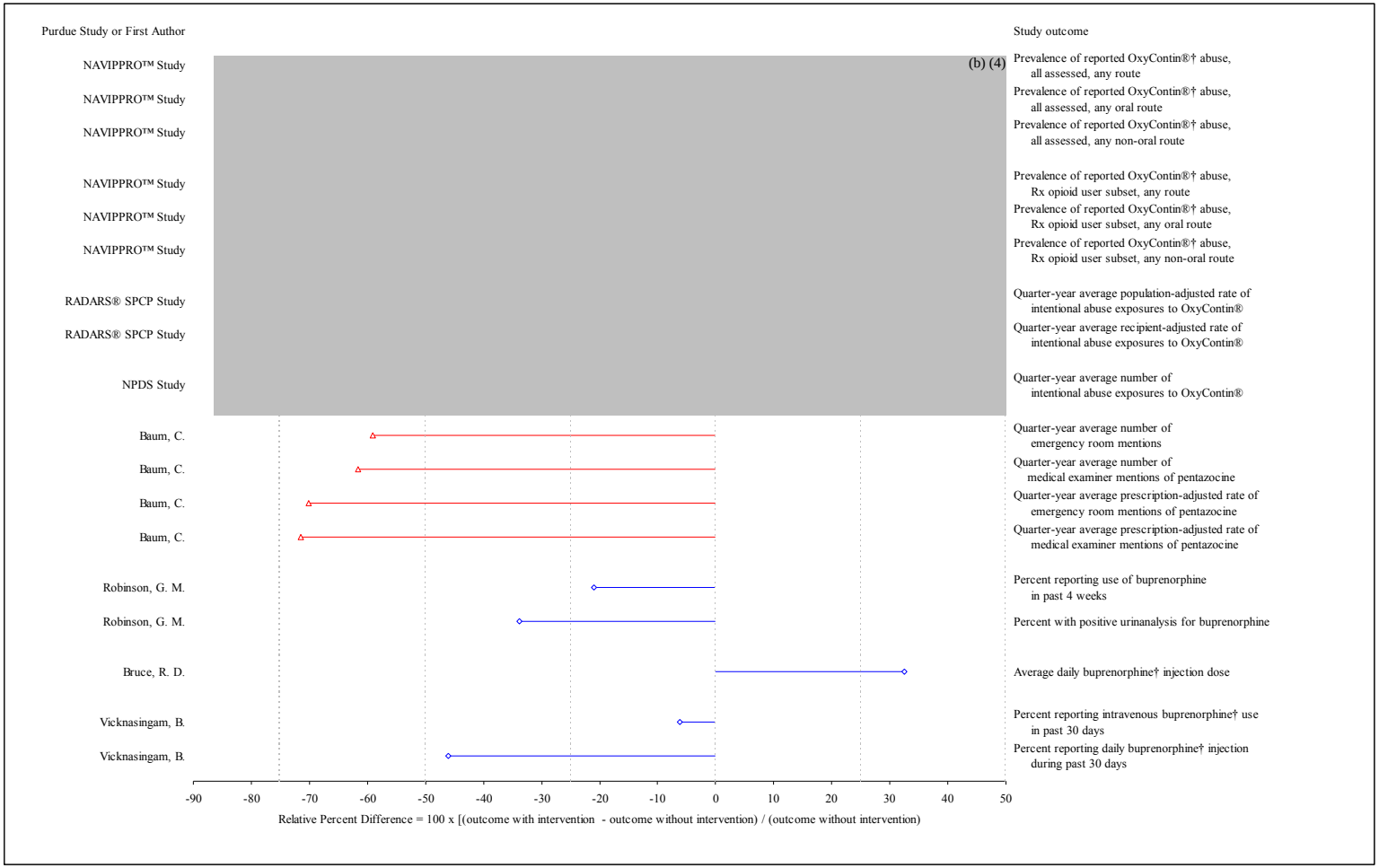
Table 33: Assessment of opioid abuse before and after marketing started for reformulated versions of OxyContin®, pentazocine, and buprenorphine

Purdue study or first author (citation)	Original / reformulated formulation	Data source	Population	Measure of drug abuse	Route of administration	Measure		Relative percent difference
						before	after	
Purdue's NAVIPPRO™	OxyContin® / reformulated OxyContin®	NAVIPPRO™ ASI-MV data stream	Individuals entering substance abuse treatment in the U.S.	Prevalence of OxyContin®† use	Any	(b) (4)		
					Any oral			
					Any non-oral			
			Individuals entering substance abuse treatment in the U.S. and who reported prescription opioid abuse	Prevalence of OxyContin®† use	Any route			
					Any oral route			
					Any non-oral			
Purdue's RADARS® SPCP	OxyContin® / reformulated OxyContin®	RADARS® System Poison Center Control Program	Individuals calling poison centers in the U.S.	Quarter-year average population-adjusted rate of intentional abuse exposures to OxyContin®	Any route			
				Quarter-year average recipient-adjusted rate of intentional abuse exposures to OxyContin®				
Purdue's NPDS	OxyContin® / reformulated OxyContin®	National Poison Data System	Individuals calling poison centers in the U.S.	Quarter-year average number of intentional abuse exposures to OxyContin®	Any route			
Baum (52)	Pentazocine / pentazocine-naloxone	DAWN – emergency room data	Individuals going to emergency rooms in the U.S. for drug abuse-related outcomes	Quarter-year average number emergency room mentions of pentazocine	Any route			
				Quarter-year average number of medical examiner mentions of pentazocine				
		DAWN – medical examiner data	Individuals who died due to drug abuse in the U.S.	Quarter-year average prescription-adjusted rate of emergency room mentions of pentazocine	Any route			
				Quarter-year average prescription-adjusted rate of medical examiner mentions of pentazocine				
Robinson (53)	Buprenorphine / buprenorphine-naloxone	Questionnaires	Patients of the Wellington Alcohol and Drug Center, Wellington, New Zealand	Percent reporting buprenorphine use in past 4 weeks	Any route	81%	64%	-21%
		Drug urine screens		Percent with positive urinalysis for buprenorphine	Any route	65%	43%	-34%
Bruce (54)	Buprenorphine / buprenorphine-naloxone	Interviews	Individuals who injected buprenorphine in Kuala Lumpur, Malaysia	Average daily buprenorphine† injection dose	Injection	1.88 mg	2.49 mg	+32%
Vicknasingam (55)	Buprenorphine / buprenorphine-naloxone	Surveys	Individuals who injected buprenorphine or buprenorphine-naloxone in Kuala Lumpur, Penang, or Johor Bahru, Malaysia	Percent reporting intravenous buprenorphine† use in past 30 days	Injection	97%	91%	-6%
				Percent reporting daily buprenorphine† injection during past 30 days	Injection	63%	34%	-46%

†Measure of drug abuse assessed after marketing started for the reformulation includes only drug abuse associated with the reformulation

Reference ID: 3292351

Figure 39: Relative percent difference in various study measures of abuse regarding abuse of OxyContin® (black line), pentazocine (red line), or buprenorphine (blue line), before versus after marketing started for reformulated versions of these opioids



†Measure of abuse assessed after marketing started for the reformulation includes only drug abuse associated with the reformulation
See also Table 33.

Question for discussion: Consider the possibility that overall (that is, not route-specific) abuse of ER oxycodone does not decrease after licit and illicit supplies of the original formulation of ER oxycodone – brand and generic – are exhausted. Can it be expected that a change in the route of administration profile of ER oxycodone abuse from primarily non-oral to primarily oral routes results in a change in clinical outcomes?

In theory, deterring ER oxycodone abuse via injection or snorting could reduce the population-risk of addiction, overdose, poisoning, death, even if overall (that is, not route specific) abuse of ER oxycodone did not decrease after marketing started for reformulated OxyContin®. However, in a real-world setting, the association between different routes of administration and these clinical outcomes is confounded by an individual's opioid tolerance and the individual's history of opioid abuse.

In theory, each route of administration has a different potential to induce addiction, and result in overdose, poisoning, and death. Specifically, reinforcement from opioids is inversely related to the rate of onset of the opioid's pharmacological action, and this rate is directly linked to route of administration (56). In general, drugs ingested through injection, smoking, and inhalation have a much more rapid onset than drugs ingested through oral routes. So, addiction potential and potential for overdose, poisoning, and death should be theoretically lower for orally administered drugs.

However, oral routes can also lead to addiction, overdose, poisoning, and death, especially if dosages are high and doses are administered more frequently. Indeed, (b) (4) of deaths reported to the RADARS® SPCP regarding prescription opioid exposures were the result of oral routes of administration (57). As noted by Katz et al., a higher percentage of RADARS® SPCP cases associated with oral routes ended in death (67/5831, or 1.15%), than cases associated with inhalation (2/321, or 0.62%), or with parenteral use (1/200, or 0.5%).

However, when considering all serious adverse events (including death), Katz et al. observed the opposite trend (57). Specifically, a higher percentage of cases associated with parenteral use ended in death or other serious adverse event (33/200, or 16.5%), than cases associated with inhalation (33/321, or 10.2%), or with oral routes (499/5831, or 8.6%).

To further complicate the issue, non-oral routes of abuse are markers for more severe opioid abuse problems in a real-world setting (57). There is a progression from ingestion among individuals with little experience with opioid abuse, to snorting and/or injection among those with more experience. For example, as described in the same article authored by Katz et al., the mortality profile for ER oxycodone does not reflect the routes of abuse profile for adults entering substance treatment centers, or for the general population of individuals who abuse drugs:

- Most of the 465 ER oxycodone-related deaths recorded in the Drug Abuse Warning Network were associated with oral routes ((b) (4) followed by injection ((b) (4) and then snorting ((b) (4)
- Among adults entering substance treatment center and reported abuse of ER oxycodone, (b) (4) of those reported ER oxycodone abuse via oral routes, injection, and snorting, respectively
- Among those in the general population of individuals who abuse drugs and specifically reported ER oxycodone abuse, (b) (4) reported ER oxycodone abuse via oral routes, injection, and snorting, respectively

Whether a shift in the route of administration profile for ER oxycodone abuse – from primarily oral routes to primarily non-oral routes – results in fewer overdoses, poisonings, and death cannot be determined at this time without additional information on clinical outcomes.

Reference ID: 3292351

Still, if a shift in the route of administration profile for ER oxycodone abuse did result in less overdose, poisoning, and death, then it may be expected that the reductions may be seen among individuals with more prescription opioid abuse experience. This is because, unlike individuals with less experience, experienced individuals are more likely to abuse via non-oral routes of administration.

On a different matter, changes in the route of administration profile for ER oxycodone abuse may result in reductions in other clinical outcomes. For example, it could be expected that less abuse via inhalation may result in less nasal and palatal necrosis and perforation (57). In addition, it could be expected that less abuse via injection may result in less cutaneous complications and viral and fungal infections (57). In the Reviewer's opinion, these hypothetical reductions were not the objective of reformulating OxyContin®, but, nonetheless, they could be beneficial secondary effects of the reformulation under the assumption that an individual intent in injecting or snorting an opioid does not shift abuse from ER oxycodone to other substances, such as heroin.

5 CONCLUSIONS

In summary, the Reviewer noted that preliminary findings from several of the investigations in Purdue's postmarketing study program are suggestive of reductions in OxyContin® abuse after the introduction of reformulated OxyContin® to the market, but these findings do not provide definitive evidence of abuse-deterrence. Indeed, it cannot be determined what the prevalence of overall (that is, not route-specific) or route-specific abuse would be in the absence of original OxyContin® abuse. Abuse of original OxyContin® persisted even though prescriptions dispensed with original OxyContin® precipitously dropped after marketing started for reformulated OxyContin®. This persistence contributed to a persistence in abuse of OxyContin® regardless of formulation. This persistence in abuse could reflect, among other things, misclassification of abuse of reformulated OxyContin® as abuse of original OxyContin®.

The Reviewer also noted that any decrease in OxyContin® abuse following the introduction of reformulated OxyContin® was mainly limited to non-oral routes of administration. Finding that non-oral abuse of the reformulation was lower than the original formulation is particularly important, since the reformulation of OxyContin® was specifically designed to deter certain non-oral routes of abuse. However, this finding on non-oral abuse is primarily supported by one investigation – the NAVIPPRO™ Investigation.

Furthermore, Purdue has not provided any robust data on the clinical outcomes of overdose, poisoning, and death, or formally assessed the clinical outcome of addiction, to support a link between changing routes of administration and these clinical outcomes.

Additional follow-up and completion of the proposed analyses are needed to appropriately evaluate the effect of the reformulation of OxyContin® on abuse and misuse. Most importantly, FDA recommends that the sponsor provide a minimum of 3 to 5 years of follow-up since marketing started for the reformulation for all investigations. This timeframe is crucial in evaluating the persistence in original OxyContin® abuse, assessing how sustainable the reductions in abuse observed in this interim report are, and completing planned analyses and assessments of clinical outcomes.

Reference ID: 3292351

6 RECOMMENDATIONS TO THE SPONSOR

The following recommendations from the FDA to the sponsor supersede the recommendations listed in a review (33) of the interim report submitted to the FDA in December 2011:

FDA has the following overarching recommendations for all eleven investigations:

1. Some analyses in the interim report are markedly different from analyses proposed in the January 2011 protocol. Therefore, by July 31, 2013, submit a final protocol for each of the investigations that incorporates the recommendations listed below, and conduct future evaluations of these investigations according to the final protocol. Also see recommendation 6.
2. Plan to analyze data on abuse and misuse of OxyContin® and comparator opioids for 3 to 5 years before and after marketing started for reformulated OxyContin®, such as from August 2005 through August 2015. This timeframe, which is longer than the initially proposed timeframes, will help evaluate whether the findings from the July 2012 interim report can be considered stable. Specifically, this timeframe will help examine whether addicts will ultimately change their abuse patterns, possibly by finding innovative ways to tamper with the new formulation of OxyContin®.
3. For both OxyContin® (stratified by formulation when applicable) and opioid comparators, provide quarter-year data on numerators, denominators, rates, standard errors and 95% confidence intervals (when applicable), study sites that contributed data anytime within each quarter-year (when applicable), and the universe from which study sites are selected (when applicable). The data may be presented graphically or numerically or both, but must be presented for the whole study period. Although a formal analysis of trends may not be sufficiently powered, presenting data on trends will help assess the appropriateness of comparing changes in average levels of abuse.
4. Section 4.12.3 of the July 2012 interim report states that adjustment for prescriptions dispensed may bias exposure rates due to 1) a lag time from prescriptions being dispensed to being abused, and 2) over-adjustment for reductions in prescriptions in which the reformulated product may have its effect. These arguments are plausible, but adjusting for measures of each opioid's availability is the only way to adequately compare OxyContin® to its comparators. Therefore, in reference to recommendation 3, the sponsor should also present quarter-year data adjusted for the appropriate at-risk population and availability of OxyContin®. See also recommendation 10.
5. Discuss findings in light of the risk evaluation and mitigation strategy (REMS) implemented in Aug 2010 for reformulated OxyContin®.
6. Use placeholders in future reports for analyses that were planned, but have not been performed. Provide an explanation for analyses that will not be performed. (Also see recommendation 1). Submit protocols and reports according to the following schedule:

a. Draft protocols	As needed before October 2013
b. Final protocol submission	October 2013
c. Interim report	January to April 2014
d. Final study report	Contingent on results for interim report

FDA recommends the following for the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Investigation; Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP) Investigation; and the National Poison Data System (NPDS) Investigation:

Reference ID: 3292351

7. Note that, among all investigations presented in the July 2012 interim report, these three investigations should be used in the fulfillment of the postmarketing requirement. If the sponsor wants other investigations that use sound epidemiological methods to be given consideration for the fulfillment of the postmarketing requirement, an explanation of how the investigation(s) fulfill each of the following criteria should be provided:

    a. The investigation assesses changes in outcomes that provide meaningful measures of abuse-deterrence.

    b. The investigation produces nationally representative data or data from a large geographic region

    c. The investigation assesses overall and route-specific abuse, misuse, or both abuse and misuse. Clinical outcomes that are <u>specifically and explicitly related</u> to abuse or misuse may be considered as well. The definition of abuse and misuse should be consistent with the definitions from the October 2010 Advisory Committee:

        <u>Abuse</u> – the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effects it produces

        <u>Misuse</u> – the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner

        For clarity, the following definition is also provided:

        <u>Medication error</u> –, any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use (according to the National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP)).

    d. The investigation has sufficient data after a suggested 3 to 5 years of follow-up after marketing started for reformulated OxyContin®. Specifically, the investigation should be sufficiently powered to assess changes in trend and level of OxyContin® abuse, misuse, or both abuse and misuse. See recommendation 2.

8. Reformulated OxyContin® and original Oxycontin® may not be the only ER oxycodone formulations abused. Analyze the following formulations of ER oxycodone:

    a. Original formulation ER oxycodone (brand + generic)
    b. All OxyContin®, that is, brand only
    c. Original OxyContin®, that is, brand name original formulation
    d. Reformulated OxyContin®
    e. Generic ER oxycodone
    f. Mexican and Canadian ER oxycodone (brand + generic)
    g. ER oxycodone, formulation unknown

9. To ensure interpretability of study results, standardize these investigations by using the seven comparators stated in Table 34. Other opioid comparators not listed in Table 34 may be used in supplemental analyses, but not in primary analyses, as long as sufficient reason for study inclusion and adequate detail on the proposed comparator is provided.

Reference ID: 3292351

Detail should include whether the comparator is a combination or single-entity (SE) product, extended-release (ER) or immediate-release (IR) formulation, product with an oral or non-oral indicated route of administration (ROA), and a prescription product or an illicit opioid or mixture of both. Comparators that use the descriptor 'other' (as in 'other opioids') require a complete description (that is, a line listing of each product considered as 'other') since it is difficult to determine exactly what 'other' refers to when used in context with three or more comparators and among the eleven investigations. Lastly, list all the active ingredients for comparators that combine two or more active ingredients.

10. To ensure interpretability of results, standardize the rates reported in these studies by using the three denominators in Table 35. Of the three denominators, FDA prefers abuse rates to be presented with extended units (e.g., tablets) as the denominator. Other denominators not listed in Table 35 may be used in supplemental analyses, but not in primary analyses, as long as sufficient reason for study inclusion and adequate detail on the proposed denominator is provided. See also recommendation 4.

11. Interpret mixed findings, particularly if findings indicate that the level of OxyContin® abuse (in terms of prevalence or rates) after marketing started for reformulated OxyContin® was higher than the level of abuse for opioid comparators, but lower than the level of original OxyContin® abuse prior to the marketing of reformulated OxyContin®.

12. Consistent with the January 2011 protocols for the NAVIPPRO™ Investigation and the RADARS® SPCP Investigation, define the transition period as 3Q2010 through 4Q2010 for all primary analyses. The first quarter of 2011 (1Q2011) should be the beginning of the study period that is used to examine opioid abuse after the introduction of reformulated OxyContin® to the market. Supplemental analyses may define the transition period differently as needed.

13. Assessment of changes in clinical outcomes is integral to the postmarketing requirement. Due to the nature of the data collection procedures for the ARGUS Investigation and an inadequate definition of abuse in the Kaiser Permanente Health System Investigation, the ARGUS Investigation and the Kaiser Permanente Health System Investigation cannot, at this time, be used to fulfill the postmarketing requirement of an assessment of changes in abuse-related clinical outcomes. Therefore, use the NAVIPPRO™ Investigation, RADARS® SPCP Investigation, and the NPDS Study to assess changes in addiction and death – see investigation-specific recommendations below.

14. Regarding the NAVIPPRO™ Investigation, FDA recommends the following:

    a. Assessment of the severity or duration of addiction could enhance the understanding of the association between the introduction of reformulated OxyContin® to the market and addiction to OxyContin® or opioids in general. Clarify if the NAVIPPRO™ Investigation can assess severity or duration of addiction (specific to OxyContin® or opioids in general) and whether an assessment would be useful in the overall postmarketing study program. If so, provide an explicit definition of 'addiction' that incorporates these features.

    b. Provide descriptive statistics comparing demographic and treatment center characteristics for centers selected for the investigation, centers not selected for the investigation, and the universe of treatment centers. Characteristics of treatment centers to compare could include:

Reference ID: 3292351

1. the prevalence of original OxyContin® abuse before marketing started for reformulated OxyContin®, or in the quarter-year immediately prior to entering the investigation
2. main funding source (public or private)
3. geographic location
4. modality of treatment (methadone-treatment, detox, etc.)

Characteristics of patients to compare could include:

1. demographics, such as age and sex
2. clinical characteristics, such as addiction severity
3. substance use characteristics, such as injection use history

c. Under the assumption that the treatment centers selected for this investigation are nationally representative and representative of all NAVIPPRO™ sites (see recommendation 14.b), one possible way to calculate extended-unit-adjusted prevalences is to:

1. Identify a fixed set of treatment centers that all capture abuse of reformulated OxyContin® by quarter-year xQ20xx (for example, 1Q2011) and provide data to NAVIPPRO continuously during the pre-formulation and post-formulation study periods (ignoring the transition period from 3Q2010 to xQ20xx).
2. Calculate prevalence per quarter-year per opioid using aggregated data, not person-level data
3. Adjust the quarter-year prevalence per opioid with the number of extended-units dispensed for opioid

Note: This calculation of prescription-adjusted prevalences does not restrict the prevalence of abuse between 0% and 100%. However, the violation is likely to be minor.

15. Regarding the RADARS® SPCP Investigation and NPDS Investigation, FDA recommends the following:

a. For better interpretability alongside the RADARS® SPCP Investigation, modify the NPDS Investigation to assess route-specific abuse (any oral vs. any non-oral, injection, inhalation, and smoking), mortality rate and case-fatality rate, and abuse stratified by each formulation.

b. Primary analyses should <u>only</u> assess changes in <u>intentional abuse exposures</u> and <u>intentional misuse exposures</u>, which are exposures whose definitions are the most consistent with the October 2010 Advisory Committee's definitions of abuse and misuse. All other types of exposure can be considered for supplemental analyses. If these supplemental analyses are pursued, then explain how these findings will affect the interpretation of findings for intentional abuse exposures and intentional misuse exposures. In particular, provide a mechanistic or biological pathway linking the reformulation of OxyContin® to changes in these types of exposure.

c. Specifically for the RADARS® SPCP Investigation, changes in the number of zip codes throughout the study period may result in a roaming denominator of

Reference ID: 3292351

population with varying abuse risk throughout the years. Primary analysis should use zip codes being covered throughout the entire study period.

d. Similar to proposed analyses for the RADARS® SPCP Investigation, use regression analysis in the NPDS Investigation to characterize levels and trends of exposures and exposure rates before and after marketing started for reformulated OxyContin®.

e. Describe how adverse reactions (in accordance with labeled, prescribed use) and withdrawal are defined and collected in NPDS.

Regarding the eight other investigations, FDA recommends the following:

16. We strongly recommend the removal of any of the eight investigations that, based solely on the investigation's methodological limitations, is not expected to provide additional context to the overall postmarketing study program. Therefore, explain how each of these eight investigations provides context to the postmarketing study program, especially with respect to the NAVIPPRO™ Investigation, RADARS® SPCP Investigation, or the NPDS Investigation. Context may include drug utilization and supply of OxyContin®, qualitative assessment of OxyContin® abuse (knowledge, attitudes, and behaviors), and assessment of mortality.

17. When applicable, we strongly advise incorporating recommendations 8, 9, 10, 11, and 12. If recommendations 8, 9, and 10 are not appropriate, explain why.

18. Regarding the Kaiser Permanente Health System Investigation, we recommend the following:

    a. Describe how the classifications of certainty of opioid involvement ('definite,' 'probable,' and 'possible') differ and how the planned analyses will incorporate these classifications into the measurement of overdoses and poisonings

19. Regarding the National Surveys Investigation, FDA recommends the following:

    a. Use descriptive statistics to compare the demographic and geographic breakdown for all three surveys.

    b. Provide a white paper or publication demonstrating the national representativeness of the RADARS® College Survey.

    c. Provide the relevant survey instruments and documentation. Clarify whether any substantive changes have been made to the survey during the study periods with respect to ascertaining OxyContin® use (including use of each formulation) and routes of administration.

    d. According to Figure 31 in the July 2012 interim report and Table 17 in the January 2011 protocol, it seems that all surveys cannot differentiate between abuse, misuse, and medication errors. Clearly explain how this investigation will contribute to the postmarketing study program in light of the discrepancy between the surveys' and October 2010 Advisory Committee's definitions of abuse and misuse. If the definitions are indeed consistent with the Advisory Committee's definitions, then provide a detailed description of how the questions from each survey will be used to create the proposed outcome with respect to the Advisory Committee's definition of abuse.

    e. Provide a complete list of proposed covariates, including definitions where necessary.

Reference ID: 3292351

f. Provide an estimation of potential respondent overlap, if any, between the surveys.

g. If the RADARS® System College Survey will be used to assess route of administration of abuse, then provide an *a priori* protocol. See recommendation 1.

h. Determine whether analyzing National Survey on Drug Use and Health by quarter-year is appropriate and, if so, analyze by year and by quarter-year.

20. Regarding the RADARS® System Drug Diversion Program Investigation, FDA recommends the following:

    a. Determine the universe of drug diversion cases and characterize the coverage of the RADARS® Drug Diversion database as compared to that universe.

    b. The population covered each year may result in a roaming denominator of populations with varying abuse risks. Consider using data from zip codes contributing data during the whole study period.

    c. If possible, develop an outcome metric that relates diverted products captured (or not captured) by law enforcement to individuals having the following outcomes of interest: abuse, misuse, addiction, overdose, and death.

    d. If possible, determine the number of filled prescription drugs or dispensed units (such as tablets) captured by law enforcement during each quarter-year of the study period.

    e. Provide a complete list of proposed covariates, including definitions where necessary.

    f. If possible, adjust the opioid street prices for inflation and geographic differences.

    g. If possible, relate the information on price per mg to price per tablet or price per prescription.

    h. If possible, stratify opioid street prices by dosage strength.

    i. Consider using overlapping zip codes to relate this investigation to any combination of the following: the NAVIPPRO™ Investigation, RADARS® SPCP Investigation, or NPDS Investigation.

21. Regarding the doctor shopping investigation, FDA recommends the following:

    a. Develop a criterion to be used in concurrent or predictive validation of doctor shopping definitions.

    b. Clarify whether the outcomes observed in the IMS LRx database can be nationally projected.

    c. Consider using overlapping zip codes to relate this investigation to any combination of the following: the NAVIPPRO™ Investigation, RADARS® SPCP Investigation, or NPDS Investigation.

Reference ID: 3292351

22. Regarding the Chat Rooms Investigation, FDA recommends the following:

    a. Provide a description of each of the websites assessed, including names and hyperlinks; statement of purpose; number of visits, threads, posts, and authors; and mean number of posts – all and initiated - per author.

    b. Clarify whether websites were included or excluded during the study period. If so, explain how the investigation will examine the effect of the changing data sources on results.

    c. Define 'recreational drug abuser' in reference to the October 2010 Advisory Committee's definition of abuse. It is not clear whether message boards that 'promote free discussion of psychoactive drug use' include non-abusers and how inclusion of non-abusers may affect results.

    d. If possible, provide a description of the websites in terms of the author's demographic information (such as age, gender, and geographic location – possibly based on IP address) and clinical information (drug use history and substance use treatment history). If geographic information is available, consider using overlapping zip codes to relate this investigation to any combination of the following: the NAVIPPRO™ Investigation, RADARS® SPCP Investigation, or NPDS Investigation.

    e. Describe how the original OxyContin® formulation, reformulated OxyContin®, OxyNeo, and other formulations are differentiated. If possible, provide data on the proportion of authors who are <u>current</u> or <u>past</u> users of each formulation and of other opioids.

    f. Describe how Web Informed Services incorporates changes in street terms for OxyContin® and comparators and if analyses with new street terms is performed on previously analyzed data.

    g. Provide the definitions for the topic categories and proportions. In particular, it is not clear what the difference is between "mixed" and "unclear" discussion categories. Since these two categories consistently have the majority of posts, this could have a large effect on the interpretability of this analysis. Furthermore, the proportion of "general discussion" is exceptionally large, so consider examining whether distinct themes are present in the "general discussion."

    h. Provide quantitative data on posts that measures whether abusers were switching to or from OxyContin® to other drugs and switching between routes of administration.

23. Regarding the Kentucky Investigation, FDA recommends the following:

    a. We recommend that this investigation be removed from the postmarketing study program for the following reasons:

        1. Findings from this investigation will not be nationally representative because the sample, which is based on convenience sampling, only includes abusers in rural eastern Kentucky who, before marketing started for reformulated OxyContin®, abused the original OxyContin® formulation

        2. It is not clear how the qualitative assessments performed in this investigation will contribute to the postmarketing study program beyond what the Chat Rooms Investigation will contribute.

Reference ID: 3292351

24. Regarding the IMS Xponent Investigation, FDA recommends the following:
    a. This investigation can provide essential context on national drug utilization of OxyContin®. The recommendations below are provided in light of recommendation 16.
    b. Determine whether the findings from the IMS Xponent Investigation for Abuse and Diversion Detection prescribers could be explained by an unstable number of prescribers during the study period.
    c. With respect to recommendation 2, continue data collection for this investigation.
25. Regarding the ARGUS Investigation, FDA recommends the following:
    a. Describe how missing information (such as lack of information on dates of death or formulation) could affect this investigation's findings, particularly regarding case reports of fatalities.

Reference ID: 3292351

Table 34: Recommended opioid comparators for the NAVIPPRO™ Investigation, RADARS® SPCP Investigation, and the NPDS Investigation

Comparator	Epidemiological Reasoning	NAVIPPRO ™	RADARS® SPCP	NPDS
Oxycodone-containing Products				
IR SE oxycodone	This contains the active ingredient of OxyContin®, but in an IR formulation	P	P	A
SE oxycodone, excluding OxyContin®	This comparator's definition is revised to IR SE oxycodone.			R
IR oxycodone-acetaminophen	Acetaminophen causes irritation when used non-orally. Therefore, this comparator may reveal a lower-bound threshold for non-oral abuse of oxycodone.	A	A	A
ER/LA SE Opioids Indicated for Oral Administration				
SE ER/LA opioids, excluding oxycodone and methadone	This will help compare OxyContin® to similar opioids with the same release mechanism and indicated route of administration. Methadone is used for opioid treatment and may have an inherently different abuse liability.	A	A	A
ER morphine	This is a suitable comparator for exploring non-oral ROA. Among clients admitted into substance abuse treatment, injection and inhalation was high for ER morphine ([(b) (4)] and [(b) (4)] respectively) and ER oxycodone ([(b) (4)] and [(b) (4)] respectively)[α].	P	A	A
ER oxymorphone	This is also a suitable comparator. Among clients admitted into substance abuse treatment, inhalation was high for ER oxymorphone ([(b) (4)] and ER oxycodone ([(b) (4)] [α].	P	A	A
Immediate-Release Combination Products, Excluding Oxycodone-Containing Combination Products				
IR hydrocodone-acetaminophen	This had the least opioid abuse liability among various opioids abused by patients entering abuse treatment. When abused, ROA was predominately oral.	A	P	A
Other Comparators				
Fentanyl transdermal or methadone	Remove for lack of comparability. Fentanyl transdermal is indicated for transdermal administration. Methadone is used in the treatment of opioid addiction.		R	
Heroin	This is an illicit drug with predominantly non-oral ROA	A	A	P

Reference ID: 3292351

Comparator	Epidemiological Reasoning	NAVIPPRO ™	RADARS® SPCP	NPDS
	(injection and inhalation).			
Other prescription opioids, including IR oxycodone, hydrocodone, fentanyl hydromorphone, morphine, oxymorphone, methadone, buprenorphine, tramadol, and tapentadol	Remove for lack of comparability. The opioids contained in this comparator are too diverse (IR and ER, single entity and combination, and indication for oral and non-oral administration) to compare against OxyContin®.		R	

P = Described in the protocol submitted on Jan 26, 2011, summary of findings submitted on Dec 23, 2011, summary of findings submitted on Jul 31, 2012, or abstracts

A = Add this comparator for better comparability between studies

R = Remove this comparator for future analyses even though it is described in the protocol submitted on Jan 26, 2011, summary of findings submitted on Dec 23, 2011, summary of findings submitted on Jul 31, 2012, or abstracts

[α] Butler, S. F., Black, R. A., Cassidy, T. A., Dailey, T. M., & Budman, S. H. (2011). Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduction Journal*, *8*(29):

Acronyms

ER = extended-release

IR = immediate release

LA = long-acting

NAVIPPRO™ = National Addictions Vigilance Intervention and Prevention Program

NPDS = National Poison Data System

RADARS® SPCP = Researched Abuse, Diversion and Addiction-Related Surveillance System Poison Center Program

ROA = route of administration

SE = single-entity

Reference ID: 3292351

Table 35: Recommended denominators for the NAVIPPRO™ Study, RADARS® SPCP Study, and the NPDS Study

Denominator	Epidemiological Reasoning	NAVIPPRO™	RADARS® SPCP	NPDS
Population (national, total in zip codes covered by database, or per target population such as opioid abusers)	The number of events reflects the size of the population from which the events arise from.	P	P	P
[Opioid] prescriptions	Each opioid prescription represents an opportunity of abuse, and therefore, this denominator adjusts for availability of each opioid for abuse. Unlike for dosage units, this denominator does not ignore the possibility that whole prescriptions may be diverted.	P	A	P
Unique patients dispensed drug [opioid]	Although this denominator partially adjusts for the availability of each opioid, other denominators (opioid prescriptions and dosage units) are more granular.		R	
Dosage units (for example, tablets) dispensed	Each dosage unit represents an opportunity of abuse, and therefore, this denominator adjusts for availability of each opioid for abuse. Unlike for opioid prescriptions, this denominator accounts for unbalanced patterns in the number of tablets prescribed per prescription of each opioid.	A	A	A

P = Described in the protocol submitted on Jan 26, 2011, summary of findings submitted on Dec 23, 2011, summary of findings submitted on Jul 31, 2012, or abstracts

A = Add this comparator for better comparability between studies

R = Remove this comparator for future analyses even though it is described in the protocol submitted on Jan 26, 2011, summary of findings submitted on Dec 23, 2011, summary of findings submitted on Jul 31, 2012, or abstracts

Acronyms

NAVIPPRO™ = National Addictions Vigilance Intervention and Prevention Program

NPDS = National Poison Data System

RADARS® SPCP = Researched Abuse, Diversion and Addiction-Related Surveillance System Poison Center Program

Reference ID: 3292351

7 APPENDIX A: REFERENCES

1. Purdue Pharma L.P. (2012). OxyContin® (oxycodone hydrochloride controlled-release) Tablets, for oral use, CII. FDA-approved labeling, *from* labeling revision for NDA 20553, supplement number 064, approved on July 9, 2012.

2. Purdue Pharma L.P. (2012). OxyContin® (oxycodone hydrochloride controlled-release) Tablets, for oral use, CII. FDA-approved labeling, *from* labeling revision for NDA 22272, supplement number 011, approved on July 9, 2012.

3. Rappaport, B. A. (2010). NDA Approval *for* OxyContin (oxycodone hydrochloride controlled-release) Tablets under NDA 022272. FDA/CDER/OND II. Submitted to DARRTS on Apr 5, 2010, for NDA #022272.

4. Purdue Pharma L.P. (2012). 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. Submitted to FDA on Jul 31, 2012, for NDA #022272: SDN 171 / eCTD 0143.

5. Mathers, P. R. & Davidson, J. A. (2012). Citizen Petition. Kleinfeld, Kaplan, and Becker, L.L.P. *on behalf of* Purdue Pharma, L.P. Submitted to FDA on Jul 18, 2012, for NDA #022272: SDN 167 / eCTD 0140.

6. Purdue Pharma L.P. (2012). A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011). Amended Dec 21, 2011. Submitted to FDA on Dec 23, 2011, for NDA #022272: SDN 146 / eCTD 0124.

7. Purdue Pharma L.P. (2011). Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death. Submitted to FDA on Jan 26, 2011, for NDA #022272: SDN 89 / eCTD 0088.

8. Rappaport, B. A. & Hertz, S. H. (2010). Advice / Information Request. FDA/CDER/OND II. Submitted to DARRTS on Dec 21, 2010, for NDA #022272.

Reference ID: 3292351

9. Rappaport, B. A. & Hertz, S. H. (2011). General Advice Letter. FDA/CDER/OND II. Submitted to DARRTS on Apr 5, 2011, for NDA #022272 and IND# 029038.

10. Rappaport, B. A. & Hertz, S. H. (2011). General Advice Letter. FDA/CDER/OND II. Submitted to DARRTS on May 19, 2011, for NDA #022272 and IND# 029038.

11. Rappaport, B. A. & Hertz, S. H. (2011). General Advice Letter. FDA/CDER/OND II. Submitted to DARRTS on May 24, 2011, for NDA #022272 and IND# 029038.

12. Purdue Pharma L.P. (2011). Purdue's Response to FDA's Information/Advice Letter (dated December 21, 2010) on Purdue's proposed Epidemiology Study Program as presented at the October DAAP Advisory Committee meeting. Submitted to FDA on Jan 26, 2011, for NDA #022272: SDN 89 / eCTD 0088.

13. Purdue Pharma L.P. (2011). Purdue's Response to FDA's General Advice Letters (dated April 5, 2011 and May 19, 2011) on the Protocols for Purdue's OxyContin Epidemiology Study Program. Submitted to FDA on Dec 1, 2011, for NDA #022272: SDN 140 / eCTD 0119.

14. Purdue Pharma L.P. (2012). Response to Request for Information: Epidemiology Data. Submitted to FDA on Oct 1, 2012, for NDA #022272: SDN 181 / eCTD 0153.

15. Purdue Pharma L.P. (2012). Response to Request for Information: Epidemiology Data. Submitted to FDA on Oct 4, 2012 for NDA #022272: SDN 182 / eCTD 0154.

16. Purdue Pharma L.P. (2011). General Correspondence. Submitted to FDA on Aug 4, 2011, for NDA #022272: SDN 105 / eCTD 0104.

17. Purdue Pharma L.P. (2012). General Correspondence: OxyContin Abstracts. Submitted to FDA on Mar 28, 2012, for NDA #022272: SDN 151 / eCTD 0129.

18. Purdue Pharma L.P. (2012). General Correspondence: OxyContin Abstracts. Submitted to FDA on Apr 18, 2012, for NDA #022272: SDN 156 / eCTD 0133.

Reference ID: 3292351

19. Purdue Pharma L.P. (2012). General Correspondence: OxyContin Abstracts. Submitted to FDA on Jul 24, 2012, for NDA #022272: SDN 169 / eCTD 0134.

20. Purdue Pharma L.P. (2012). General Correspondence: OxyContin Abstracts. Submitted to FDA on Aug 31, 2012, for NDA #022272: SDN 175 / eCTD 0146.

21. Purdue Pharma L.P. (2012). General Correspondence: Corrected Cover Letter for OxyContin Abstracts. Submitted to FDA on Sep 11, 2012, for NDA #022272: SDN 177 / eCTD 0149.

22. Purdue Pharma L.P. (2012). NDA Annual Report. Submitted to FDA on Jun 4, 2012, for NDA #022272: SDN 158 / eCTD 0135.

23. Purdue Pharma L.P. (2012). General Correspondence: OxyContin Abstracts. Submitted to FDA on Oct 12, 2012, for NDA #022272: SDN 183 / eCTD 0156.

24. Purdue Pharma L.P. (2012). Response to Request for Information: Epidemiology Data. Submitted to FDA on Oct 24, 2012 for NDA #022272: SDN 188 / eCTD 0157.

25. Purdue Pharma L.P. (2012). Response to Request for Information: Epidemiology Data. Submitted to FDA on Dec 4, 2012 for NDA #022272: SDN 190 / eCTD 0160.

26. Purdue Pharma L.P. (2012). Response to Request for Information: Epidemiology Data. Submitted to FDA on Dec 20, 2012, for NDA #022272: SDN 194 / eCTD 0164.

27. Purdue Pharma L.P. (2012). General Correspondence: OxyContin Abstract. Submitted to FDA on Dec 13, 2012, for NDA #022272: SDN 193 / eCTD 0162.

28. Purdue Pharma L.P. (2013). Response to Request for Information: Epidemiology Data. Submitted to FDA on Feb 22, 2013, for NDA #022272: SDN 201 / eCTD 0170.

29. Kornegay, C. (2010). *Evaluation of Preliminary Proposals and Presentations of Abuse Deterrent Studies for extended release OxyContin® and Embeda®.*

Reference ID: 3292351

FDA/CDER/OSE. Submitted to DARRTS on Dec 9, 2010, for NDA #022272 and NDA #022321.

30. McEvoy, B. (2011). Statistical Review and Evaluation of OxyContin (oxycodone hydrochloride). FDA/CDER/OTS/OB. Submitted to DARRTS on May 4, 2011, for NDA #022272.

31. Kornegay, C. (2011). Evaluation of Protocol for Abuse-Deterrence Studies. FDA/CDER/OSE. Submitted to DARRTS on Mar 18, 2011, for NDA #022272.

32. Kornegay, C. (2011). Evaluation of Six Protocols for Abuse-Deterrence Studies on Continued Release OxyContin. FDA/CDER/OSE. Submitted to DARRTS on May 13, 2011, for NDA #022272.

33. Trinidad, J. & Dormitzer, C. (2012). Review of "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011)". FDA/CDER/OSE. Submitted to DARRTS on Apr 27, 2012, for NDA #022272.

34. Frimpong, E. (2012). Statistical Review and Evaluation. FDA/CDER/OTS/OB. Submitted to DARRTS on Nov 9, 2012, for NDA #022272.

35. Zhang, R. (2013). Statistical Review and Evaluation. FDA/CDER/OTS/OB. Submitted to DARRTS on Mar 20, 2013, for NDA #022272.

36. Zhang, R. (2012). Statistical Review and Evaluation. FDA/CDER/OTS/OB. Submitted to DARRTS on Nov 5, 2012, for NDA #022272.

37. Wu, Y. (2013). Statistical Review and Evaluation. FDA/CDER/OTS/OB. Submitted to DARRTS on Feb 27, 2013, for NDA #022272.

38. U.S.Department of Health and Human Services / Food and Drug Administration / Center for Drug Evaluation and Research. (2013). Guidance for Industry: Abuse-Deterrent Opioids - Evaluation and Labeling (Draft Guidance).

39. Lapteva, L. (2010). Regulatory History of Development of Abuse Deterrent Formulations. From the October 21-22, 2010 Meeting of the Anesthetic and Life Support Drugs Advisory Committee. FDA/CDER.

Reference ID: 3292351

40. National Coordinating Council for Medication Error Reporting and Prevention. (2012). About Medication Errors: Definition. Retrieved on Oct 10, 2012, from http://www.nccmerp.org/aboutMedErrors.html.

41. Bronstein, A. C., Spyker, D. A., Cantilena, L. R., Jr., Green, J. L., Rumack, B. H., & Dart, R. C. (2011). 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clinical toxicology (Philadelphia, Pa.), 49,* 910-941.

42. Dunn, K. M., Saunders, K. W., Rutter, C. M., Banta-Green, C. J., Merrill, J. O., Sullivan, M. D. et al. (2010). Opioid prescriptions for chronic pain and overdose: a cohort study. *Annals of internal medicine, 152,* 85-92.

43. Hall, A. J., Logan, J. E., Toblin, R. L., Kaplan, J. A., Kraner, J. C., Bixler, D. et al. (2008). Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA., 300,* 2613-2620.

44. Office of National Drug Control Policy. (2011). National Drug Control Strategy. Retrieved on Nov 15, 2012, from http://www.whitehouse.gov/sites/default/files/ondcp/ndcs2011.pdf.

45. Cepeda, M. S., Fife, D., Chow, W., Mastrogiovanni, G., & Henderson, S. C. (2012). Assessing Opioid Shopping Behaviour: A Large Cohort Study from a Medication Dispensing Database in the US. *Drug safety : an international journal of medical toxicology and drug experience, 35,* 325-334.

46. Brewer, T. & Colditz, G. A. (1999). Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. *JAMA : the journal of the American Medical Association, 281,* 824-829.

47. Substance Abuse and Mental Health Services Administration. (2010). Results from the 2009 National Survey on Drug Use and Health. Volume 1: Summary of National Findings. U.S. Department of Health and Human Services / Substance Abuse and Mental Health Services Administration / Office of Applied Studies.

48. Purdue Pharma L.P. (2011). OxyContin® (oxycodone hydrochloride controlled-release) Tables: REMS One Year Assessment Report for NDA 022272, March 2011. Submitted to FDA on Mar 22, 2011, for NDA #022272: SDN 95 / eCTD 0094.

49. Purdue Pharma L.P. (2012). OxyContin® REMS Assessment 8: OxyContin Utilization Patterns Including Opioid-tolerant Utilization Patterns Before and

Reference ID: 3292351

After Implementation of the REMS. Submitted to FDA on Jul 25, 2012, for NDA #022272: SDN 170 / eCTD 0142.

50. Roca, R. & Sullivan, M. W. (2010). NDA Approval *for* Suboxone (buprenorphine and naloxone) Sublingual Film under NDA 022410. FDA/CDER/OND II. Submitted to DARRTS on Aug 30, 2010, for NDA #022410.

51. Cicero, T. J., Inciardi, J. A., Adams, E. H., Geller, A., Senay, E. C., Woody, G. E. et al. (2005). Rates of abuse of tramadol remain unchanged with the introduction of new branded and generic products: results of an abuse monitoring system, 1994-2004. *Pharmacoepidemiology and drug safety, 14,* 851-859.

52. Baum, C., Hsu, J. P., & Nelson, R. C. (1987). The impact of the addition of naloxone on the use and abuse of pentazocine. *Public health reports (Washington, D.C.: 1974), 102,* 426-429.

53. Robinson, G. M., Dukes, P. D., Robinson, B. J., Cooke, R. R., & Mahoney, G. N. (1993). The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. *Drug and alcohol dependence, 33,* 81-86.

54. Bruce, R. D., Govindasamy, S., Sylla, L., Kamarulzaman, A., & Altice, F. L. (2009). Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. *The American journal of drug and alcohol abuse, 35,* 68-72.

55. Vicknasingam, B., Mazlan, M., Schottenfeld, R. S., & Chawarski, M. C. (2010). Injection of buprenorphine and buprenorphine/naloxone tablets in Malaysia. *Drug and alcohol dependence, 111,* 44-49.

56. Compton, W. M. & Volkow, N. D. (2006). Abuse of prescription drugs and the risk of addiction. *Drug Alcohol.Depend., 83 Suppl 1,* S4-S7.

57. Katz, N., Dart, R. C., Bailey, E., Trudeau, J., Osgood, E., & Paillard, F. (2011). Tampering with prescription opioids: nature and extent of the problem, health consequences, and solutions. *The American journal of drug and alcohol abuse, 37,* 205-217.

58. Showalter, C. V. (1980). T's and blues. Abuse of pentazocine and tripelennamine. *JAMA : the journal of the American Medical Association, 244,* 1224-1225.

Reference ID: 3292351

59. Lange, W. R. & Jasinski, D. R. (1986). The clinical pharmacology of pentazocine and tripelennamine (T's and Blues). *Advances in alcohol & substance abuse, 5,* 71-83.

60. Poklis, A. (1984). Decline in abuse of pentazocine/tripelennamine (T's and Blues) associated with the addition of naloxone to pentazocine tablets. *Drug and alcohol dependence, 14,* 135-140.

Reference ID: 3292351

8 APPENDIX B: ACRONYMS AND THEIR DEFINITIONS

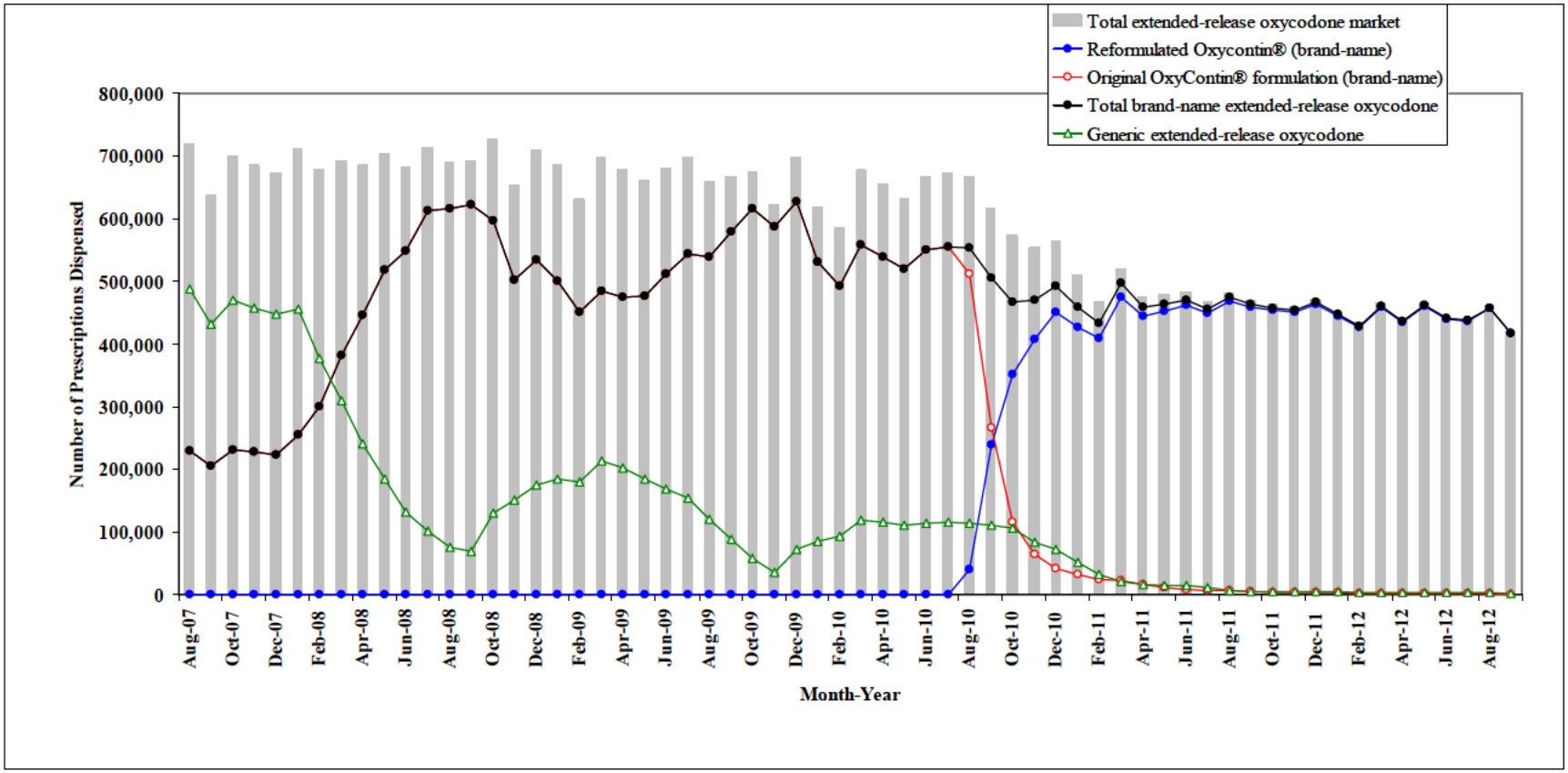
Table 36: List of Acronyms

Acronym	Definition
#HYYYY (such as 1H2011)	First or second half of year YYYY
#QYYYY (such as 1Q2011)	First / second / third / fourth quarter of year YYYY
ADD	Abuse and Diversion Detection
ARGUS	Purdue's International Drug Safety Database
ASI-MV®	Addiction Severity Indicator – Multimedia Version
CHAT™	Comprehensive Health Assessment for Teens
ER	Extended-release
IR	Immediate-release
LA	Long-acting
KP	Kaiser Permanente
MTF	Monitoring the Future
NAVIPPRO™	National Addictions Vigilance Intervention and Prevention Program
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
RADARS®	Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System
RADARS-CS	RADARS® System College Survey
RADARS® SPCP	RADARS® System Poison Center Program
ROA	Route of administration
SAMHSA	Substance Abuse and Mental Health Services Administration
SE	Single entity
TEDS	Treatment Episode Data Set
VONA	Vector One®: National

Reference ID: 3292351

9 APPENDIX C: DRUG UTILIZATION OF EXTENDED-RELEASE OXYCODONE, INCLUDING BRAND-NAME OXYCONTIN®

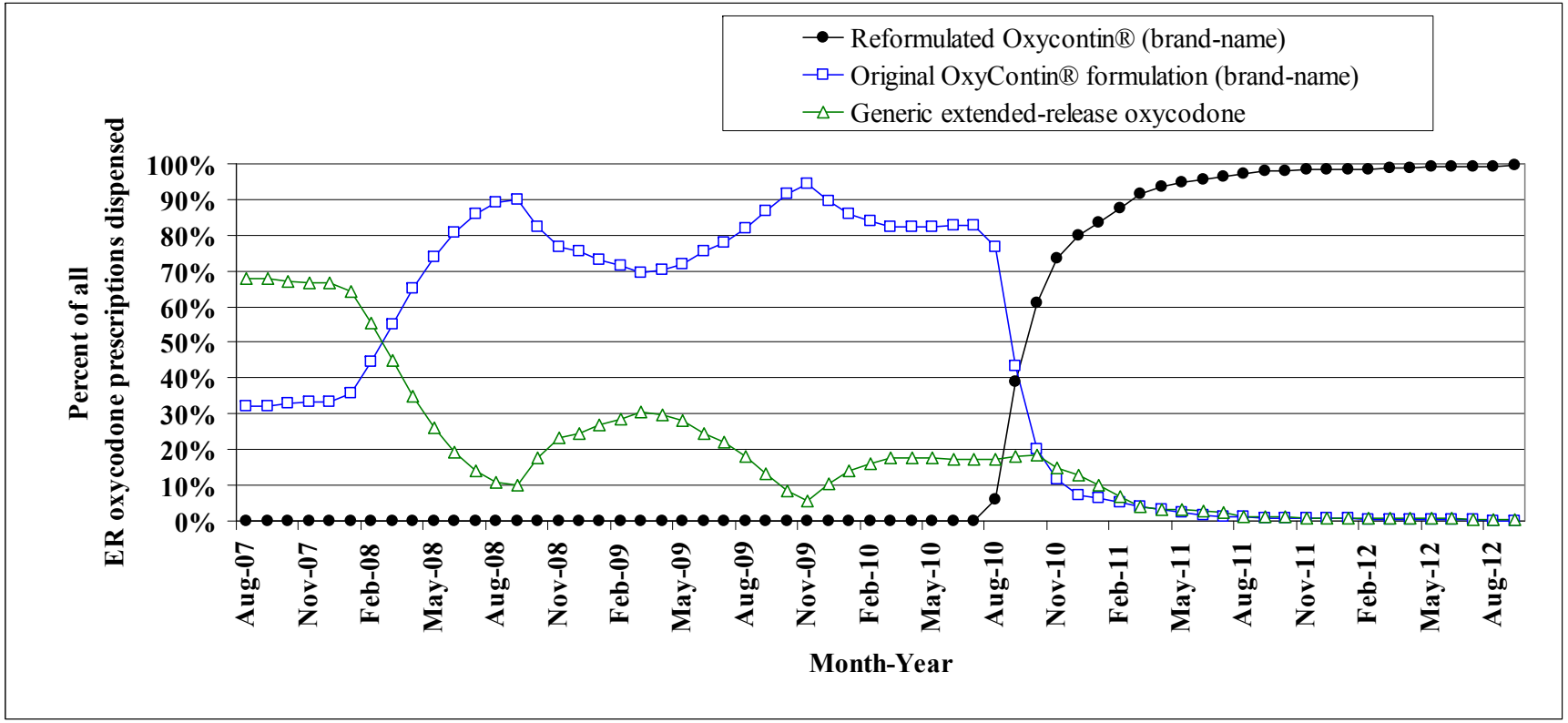
Figure 40a: Number of generic and brand-name extended-release oxycodone prescriptions dispensed each month from August 2007 to August 2012



Data source: IMS Health, Vector One®: National (VONA), Extracted November 2012.

Reference ID: 3292351

Figure 40b: Marketshare of generic and brand-name extended-release oxycodone prescriptions dispensed each month from August 2007 to August 2012



Data source: IMS Health, Vector One®: National (VONA), Extracted November 2012.

10 APPENDIX D: NAVIPPRO™ INVESTIGATION ILLUSTRATION OF ROUTES OF ABUSE PATTERNS FOR ORIGINAL AND REFORMULATED OXYCONTIN®

Figure 41a: Percent of adults who reported abuse via oral and non-oral routes of administration, among those who abused original OxyContin®, before (3Q2009-2Q2010) and after (3Q2010-3Q2012) marketing started for reformulated OxyContin®

(b) (4)

Figure 41b: Percent of adults who reported abuse via oral and non-oral routes of administration, among those who abused reformulated OxyContin®, before (3Q2009-2Q2010) and after (3Q2010-3Q2012) marketing started for reformulated OxyContin®

(b) (4)

Reference ID: 3292351

11 APPENDIX E: EXPOSURE DEFINITIONS IN RADARS® SPCP INVESTIGATION AND NPDS INVESTIGATION

Intentional exposures are defined as a purposeful action that results in an exposure. The following four categories relate to intentional exposures:

1. Intentional-Suspected suicidal: An exposure resulting from the inappropriate use of a substance for self-destructive or manipulative reasons. Cases included are suicides, suicide attempts, and suicide gestures, whether suspected or confirmed, cases in which history indicates patient was upset or depressed, patients who provide explanations for their actions such as "arguing with parents," "disturbed about poor grades," or "having marital problems", ingestions of large quantities of one or more drugs where the only likely explanation is the patient's intent to harm himself.
2. Intentional-Misuse: An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect. Case included are a person deliberately mixes or applies a pesticide inappropriately so it will be more effective, a person deliberately increases the dosage of a medication to enhance its therapeutic effect, overuse of caffeine to study for an exam.
3. Intentional-Abuse: An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect. Recreational use of a substance for any effect should be coded here. Cases included are a person who inhales helium to talk funny, a person who uses GHB at a dance club, an infant with toxic effects or withdrawal symptoms as a result of the mother's drug abuse while the child was in utero or while breast-feeding.
4. Intentional-Unknown: Exposure determined to be intentional but the specific motive is unknown.

Unintentional exposures are defined as an exposure that results from an unforeseen or unplanned event. For example, a child gaining access to a toxic substance, when it is obvious the child did not realize the danger of the action, is an unintentional exposure. The following eight coding options are available for unintentional exposures.

1. Unintentional-General: All unintended exposures that are not specifically defined below. Most unintentional exposures in children should be coded here. Cases include a toddler got into (and swallowed) a grandparent's prescription medicine, a bottle of drain opener left under the sink, or the entire contents of a container of chewable multivitamins.
2. Unintentional - Environmental: Any passive, non-occupational exposure that results from contamination of air, water or soil. Environmental exposures are usually, but not always, caused by human-made contaminants.
3. Unintentional-Occupational: Exposure that occurs as a direct result of the person being on the job or in the workplace.
4. Unintentional-Therapeutic error: An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance. Only include medications or products substituted for medications. Drug interactions (or drug/food interactions) resulting from unintentional administration of drugs/foods which are known to interact are be included.

Reference ID: 3292351

5. Unintentional-Misuse: Unintentional improper or incorrect use of a non-pharmaceutical substance. Unintentional misuse differs from intentional misuse in that the exposure was unplanned or not foreseen by the patient.
6. Unintentional - Bite/sting: All animal bites and stings.
7. Unintentional - Food poisoning: All suspected or confirmed food poisoning exposures.
8. Unintentional - Unknown: An exposure determined to be unintentional but the exact reason is unknown.

Data Source: Section 4.11.2.1 of the interim report entitled "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011): November 2011 (Amended December 21, 2011)"

Reference ID: 3292351

12 APPENDIX F: EXTENDED-RELEASE (ER) OXYCODONE FORMULATIONS ASSESSED BY THE RADARS® SYSTEM POISON CENTER PROGRAM AND THE NATIONAL POISON DATA SYSTEM (NPDS)

Table 37: Oxycodone formulations captured by RADARS® System Poison Center Program and NPDS

(b) (4)

1 Page Has Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

Reference ID: 3292351

(b) (4)

Data Source: Table 5 of Purdue's response to FDA's Information Request, dated Feb 20, 2013.

Reference ID: 3292351

13 APPENDIX G: CASE DEFINITIONS IN KAISER PERMANENTE HEALTH SYSTEM INVESTIGATION

Table 38a: Codes used in the Kaiser Permanente Health System Investigation to identify opioid-related poisonings

(b) (4)

[redacted]

Data Source: Appendix A for the interim report entitled "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"

Reference ID: 3292351

Table 38b: Codes used in the Kaiser Permanente Health System Investigation to identify opioid-related overdoses†

(b) (4)

Data Source: Table 11 of the interim report entitled "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011): November 2011 (Amended December 21, 2011)"

Reference ID: 3292351

14 APPENDIX H: MEDDRA CODES USED IN THE ARGUS INVESTIGATION TO IDENTIFY RELEVANT ADVERSE EVENT REPORTS

Table 39a: MedDRA (V 14.0) preferred terms / SMQ for drug abuse

Accidental overdose
Dependence
Disturbance in social behaviour
Drug abuse
Drug abuser
Drug administered at inappropriate site
Drug dependence
Drug dependence, antepartum
Drug dependence, postpartum
Drug detoxification
Drug level above therapeutic
Drug level increased
Drug screen positive
Drug screen
Drug tolerance decreased
Drug tolerance increased
Drug tolerance
Intentional overdose
Maternal use of illicit drugs
Multiple drug overdose accidental
Multiple drug overdose intentional
Multiple drug overdose
Needle track marks
Neonatal complications of substance abuse
Overdose
Polysubstance dependence
Substance abuse
Substance abuser
Substance use

Table 39b: MedDRA (V 14.0) preferred terms / SMQ for overdose

Accidental overdose
Drug level above therapeutic
Drug level increased
Intentional overdose
Multiple drug overdose

Reference ID: 3292351

Multiple drug overdose accidental
Multiple drug overdose intentional
Overdose
Radiation overdose
Therapeutic agent toxicity
Toxicity to various agents

Table 39c: MedDRA (V 14.0) preferred terms / SMQ for intentional misuse

Intentional drug misuse

Table 39d: MedDRA (V 14.0) preferred terms / SMQ for intentional misuse

Accidental drug intake by child
Accidental exposure
Circumstance or information capable of leading to medication error
Documented hypersensitivity to administered drug
Drug administered at inappropriate site
Drug administered in wrong device
Drug administered to patient of inappropriate age
Drug administration error
Drug dispensing error
Drug dose omission
Drug exposure via breast milk
Drug label confusion
Drug name confusion
Drug prescribing error
Expired drug administered
Inappropriate schedule of drug administration
Incorrect dose administered
Incorrect dose administered by device
Incorrect drug administration duration
Incorrect drug administration rate
Incorrect drug dosage form administered
Incorrect route of drug administration
Incorrect storage of drug
Intercepted drug administration error
Intercepted drug dispensing error
Intercepted medication error
Labeled drug-disease interaction medication error
Labeled drug-drug interaction medication error
Labeled drug-food interaction medication error
Medication error

Reference ID: 3292351

Poor quality drug administered
Radiation exposure
Radiation underdose
Underdose
Vaccination error
Wrong drug administered
Wrong technique in drug usage process

Reference ID: 3292351

15 APPENDIX I: NON-SYSTEMATIC REVIEW OF STUDIES ASSESSING THE ASSOCIATION BETWEEN OPIOIDS WITH AND WITHOUT NALOXONE AND OPIOID DRUG ABUSE

The Reviewer conducted a non-systematic review of the medical literature to identify interventions – such as marketing of a proposed abuse deterrent formulation – that have been associated with reductions in opioid abuse. The Reviewer then focused on articles that had the following characteristics:

- The study outcome was reported opioid drug abuse or clinical events indicative of opioid drug abuse.
- The intervention was clearly stated.
- The study compared how the study outcome differed among study subjects exposed or unexposed to the intervention.
- The study population was comparable before and after implementation of the intervention.
- The study found a positive result, that is, reductions in opioid drug abuse or clinical event indicative of opioid drug abuse.

The Reviewer will not provide further details on the excluded studies because the search was not systematic. Furthermore, some studies included in this review did not meet all five bulleted characteristics.

The Reviewer identified four studies that assessed how abuse changed after marketing started for a reformulated opioid and distribution of the original opioid formulation ceased. The original opioids and their reformulated versions are:

- pentazocine and pentazocine-naloxone
- buprenorphine and buprenorphine-naloxone

Pentazocine and naloxone

Pentazocine tablets are:

- opiate agonist-antagonist analgesics
- indicated for oral administration
- indicated for moderate to severe pain

Abuse of pentazocine in the U.S. grew in the late 1960s and 1970s. In 1965, the World Health Organization's Expert Committee on Dependence-Producing Drugs reviewed the available evidence on pentazocine abuse and concluded that there was little likelihood of pentazocine abuse (52). The committee also concluded that there was no need at that time for narcotic control of pentazocine internationally. FDA did not list pentazocine (brand name Talwin) under the Federal Controlled Substances Act when FDA approved pentazocine in 1967. In the late 1970s, pentazocine abuse rose concurrently with decreases in the supply and potency of heroin and increases in the cost of heroin (58). In 1979, FDA listed pentazocine as a Schedule IV substance under the Federal Controlled Substances Act (52).

Similar to OxyContin®, abuse of pentazocine occurs via oral and non-oral routes of administration. The co-injection of pentazocine with the antihistamine tripelennamine results in

Reference ID: 3292351

a euphoria similar to heroin and less dysphoric effects associated with injection of pentazocine alone[l] (59; 60).

On December 16, 1982, FDA approved the opioid agonist-antagonist combination pentazocine-naloxone (brand name Talwin NX), aiming to curb abuse of pentazocine (52).

Naloxone is an opioid antagonist that has no pharmacologic activity when ingested, but will antagonize the effects of pentazocine when used via injection.

Distribution of single-entity pentazocine tablets ceased in January 1983, and distribution of the pentazocine-naloxone tablets started in April 1983.

The study by Baum et al. reviewed use and abuse patterns of pentazocine before and after marketing started for pentazocine-naloxone (52).

This study used emergency room and medical examiner data, both from the Drug Abuse Warning Network (DAWN), and prescription data from the National Prescription Audit. In brief, DAWN[m]

- was sponsored at the time by the National Institute on Drug Abuse
- collected data from a non-random samples of emergency rooms and medical examiners, on mentions of drugs associated with abuse episodes
- did not have nationally projected data

The study only used data originating from emergency rooms and medical examiners that participated in DAWN before and after marketing started for pentazocine-naloxone.

The data on prescriptions dispensed for pentazocine and pentazocine-naloxone came from the National Prescription Audit. Data on prescriptions dispensed were nationally projected.

Baum et al. compared the quarter-year average number and quarter-year prescription-adjusted rate of pentazocine abuse mentions before versus after marketing started for pentazocine-naloxone. The period before marketing started was the first quarter of 1981 (1Q1981) to the first quarter of 1983 (1Q1983), and the period after marketing started was from 2Q1983 to 1Q1984.

The study did <u>not</u>

- differentiate between pentazocine formulations after marketing started for pentazocine-naloxone
- assess changes in abuse of other opioids
- test whether changes in the level of pentazocine mentions were statistically significant
- state the inferential statistics used to examine the trend in prescription-adjusted mentions after marketing started for pentazocine-naloxone

The study found that pentazocine mentions from emergency rooms and medical examiners decreased after marketing started for pentazocine-naloxone. Specifically, before marketing started, the quarter-year average number of pentazocine mentions from emergency rooms and medical examiners was about 520 and 12 mentions, respectively. After marketing started, this average dropped to roughly 213 and 5 mentions, respectively. The relative percent reduction in

---

[l] Abuse of both pentazocine and tripelennamine was commonly referred to as the "T's and Blues," in reference to the pentazocine's brand-name (Talwin and blue 50-mg tripelennamine tablets.

[m] The methodology used to collect and analyze DAWN data has changed considerably since publication of this study. See www.samhsa.gov for more information

Reference ID: 3292351

the average number of pentazocine mentions from emergency rooms and medical examiners was 59% and 62%, respectively.

Decreases in pentazocine mentions were particularly apparent because prescriptions dispensed with pentazocine observably increased after marketing started for pentazocine-naloxone (Figure 42, Figure 43a, and Figure 43b). The quarter-year average prescription-adjusted rate of pentazocine mentioned in emergency rooms fell 70% from 604 mentions per million prescriptions dispensed to 180 mentions per million prescriptions. Similarly, the quarter-year average prescription-adjusted rate of pentazocine mentioned by medical examiners fell 71% from 14 mentions per million prescriptions dispensed to 4 mentions per million prescriptions.

Figure 42: Number of pentazocine-naloxone (brand name Talwin Nx) and other pentazocine prescriptions dispensed in the U.S., before (1Q1981-1Q1983) and after (2Q1983-1Q1985) marketing started for pentazocine-naloxone

Copyright Material

Reference ID: 3292351

Figure 43a: Prescription-adjusted rate of emergency room mentions for pentazocine (brand name Talwin) or pentazocine-naloxone (brand name Talwin Nx) in the U.S., according to Drug Abuse Warning Network data, before (1Q1981-1Q1983) and after (2Q1983-1Q1985) marketing started for pentazocine-naloxone

Copyright Material

Figure 43b: Prescription-adjusted rate of medical examiner mentions of pentazocine (brand name Talwin) or pentazocine-naloxone (brand name Talwin Nx) in the U.S., according to Drug Abuse Warning Network data, before (1Q1981-1Q1983) and after (2Q1983-1Q1985) marketing started for pentazocine-naloxone

Copyright Material

The prescription-adjusted rate of emergency room mentions for pentazocine declined over time from 2Q1983 to 1Q1985 ($p = 0.01$). The prescription-adjusted rate of medical examiner mentions also declined during this same time period, but the trend was not statistically significant ($p = 0.09$). Baum et al. could not estimate the trend in prescription-adjusted mentions for the period before marketing started for pentazocine-naloxone because the data during this period was too scattered.

Buprenorphine and naloxone

Buprenorphine tablets and film strips are

- opiate agonist-antagonist analgesics
- indicated for sublingual administration since bioavailability of buprenorphine is low when ingested
- indicated for maintenance treatment of opioid dependence

In the U.S., FDA approved

- injectable buprenorphine (brand name Buprenex®) on December 29, 1981
- sublingual buprenorphine tablets (brand name Subutex®) on October 8, 2002
- sublingual buprenorphine-naloxone tablets (brand name Suboxone® on October 8, 2002
- transdermal buprenorphine (brand name Butrans®) June 30, 2010
- sublingual buprenorphine film (brand name Suboxone®) on August 30, 2010

Similar to OxyContin®, abuse of buprenorphine occurs via oral and non-oral routes of administration. Naloxone is an opioid antagonist that has no pharmacologic activity when ingested, but will antagonize the effects of buprenorphine when used via injection.

The Reviewer identified three studies comparing abuse of single-entity buprenorphine to abuse of buprenorphine-naloxone.

The first study, which by Robinson et al. conducted, aimed to determine prevalence of misuse of buprenorphine and buprenorphine-naloxone in Wellington, New Zealand (53).

In New Zealand, buprenorphine tablets were launched in April 1982, and, in April 1991, buprenorphine-naloxone combination tablets were launched concurrently with the withdrawal of buprenorphine.

This study assessed buprenorphine use among patients presenting or representing with opioid dependency at the Wellington Alcohol and Drug Centre. The study's analyses only included patients consenting to the study.

The Centre conducted one questionnaire before marketing started for buprenorphine-naloxone, and one questionnaire after marketing started. Specifically, the center's clinic staff conducted the first questionnaire from January 1990 to December 1990, and the second questionnaire for each month from June 1991 to May 1992.

The both questionnaires assessed self-reported use of single-entity buprenorphine, buprenorphine-naloxone combination, and buprenorphine regardless of formulation in the past four weeks. The questionnaires also assessed the routes of administration used to use buprenorphine and the reason for buprenorphine use.

Additionally, this study conducted urine drug screens to detect the presence of buprenorphine.

Reference ID: 3292351

The percent of patients reporting use of buprenorphine in the past four weeks was lower after marketing started for buprenorphine-naloxone. Specifically, 44 out of 54 patients (81%) reported use of buprenorphine before marketing started, and 28 out of 44 patients (64%) reported use of buprenorphine regardless of formulation after marketing started. The 28 patients who reported buprenorphine use after marketing started used buprenorphine-naloxone (n=11), buprenorphine only (n=3), or both buprenorphine-naloxone and buprenorphine (n=14).

Drug urine analyses also found that the percent of patients testing positive for buprenorphine use was lower after marketing started for buprenorphine-naloxone. Specifically, 26 out of 40 patients (65%) with urine drug screens tested positive for buprenorphine before marketing started, and 13 out of 43 patients (43%) tested positive for buprenorphine after marketing started.

Buprenorphine or buprenorphine-naloxone use could have been either misuse or abuse, or both. Reported reason of use included ameliorating withdrawal (63% of patients in both questionnaires) and providing euphoria (28% and 22% of patients in the first and second questionnaire, respectively). Furthermore, according to the second questionnaire, use of buprenorphine-naloxone via injection was quite high, but the authors did not provide sufficient information to determine whether buprenorphine use via injection was higher or lower after marketing started for buprenorphine-naloxone.

The second study, which Bruce et al. conducted, aimed to ascertain if the introduction of buprenorphine-naloxone to the Malaysian market resulted in a decrease in the dose of buprenorphine injected (54).

In Malaysia, buprenorphine tablets were licensed in 2003, and, in January 2007, buprenorphine-naloxone combination tablets were licensed concurrently with the withdrawal of buprenorphine. The Malaysian government also implemented a multi-pronged strategy alongside the licensing of buprenorphine-naloxone, including mandatory training about buprenorphine treatment and a national registry of patients.

The study assessed buprenorphine use among individuals from within Kuala Lumpur, Malaysia, who self-reported buprenorphine injection and demonstrated facility with buprenorphine injection practices. From these individuals, the authors used snowball recruitment strategy to recruit additional subjects.

The study used interviews conducted in January 2007 to ascertain the milligram dose of buprenorphine-naloxone injected at the time of the interview, and the prior dose of buprenorphine alone.

The authors did not describe the statistical test used to determine whether the dose of buprenorphine injection changed before versus after marketing started for buprenorphine-naloxone.

According to 41 subjects who reported buprenorphine-naloxone, the average dose used to inject buprenorphine-naloxone was more than the average dose used to inject buprenorphine alone. The mean dose of buprenorphine injection before marketing started for buprenorphine-naloxone was 1.88 mg/day, and the mean dose of buprenorphine-naloxone injection after marketing started was 2.49 mg/day. The difference in these average doses was not statistically significant ($p = 0.23$).

The third study, which Vicknasingam et al. conducted, aimed to obtain evidence and data on the misuse of buprenorphine and buprenorphine-naloxone from Malaysians who active used drugs (55).

The study used two surveys to assess whether survey participants injected buprenorphine in the past 30 days, every day in the past 30 days, and ever in the participants' lifetime. The surveys also assessed reason for injecting buprenorphine.

Reference ID: 3292351

The study included surveys conducted before and after marketing started for buprenorphine-naloxone. The first survey was conducted from October 31, 2006, to November 24, 2006. The second survey was conducted from June 1, 2007, to September 30, 2007.

The study used snowball sampling to recruit survey participants. All participants were from either Kuala Lumpur, Penang, or Johor Bahru, Malaysia, and were not in drug use treatment. The inclusion criteria for participation in the first survey was past week intravenous injection of buprenorphine, ascertained by self-report and verified by examination of recent injection marks. The inclusion criterion for the second survey was buprenorphine or buprenorphine-naloxone injection at least once in the participants' lifetime.

Results of the surveys were presented as descriptive statistics.

The percent of participants reporting intravenous buprenorphine use was lower after marketing started for buprenorphine-naloxone. Specifically, 268 out of 276 participants (97%) of the first survey reported injecting buprenorphine in the past 30 days, and 174 (63%) reported daily injections of buprenorphine in the past 30 days. In the second survey, 186 out of 204 participants (91%) reported injecting buprenorphine-naloxone in the past 30 days, and 69 (34%) reported daily injections of buprenorphine-naloxone in the past 30 days.

Injection of buprenorphine or buprenorphine-naloxone was both misuse and abuse. When asked about the <u>most important reason</u> for injecting buprenorphine, many participants of the first survey reported injecting buprenorphine for pleasure (42% of participants), followed by treatment for addiction (33%), and alleviation of withdrawal (17%). When asked about the <u>three most important reasons</u> for injecting buprenorphine, participants of the second survey reported injecting buprenorphine-naloxone to treat addiction (81%), to alleviate withdrawal (70%), because it is cheaper than heroin (57%), and for pleasure (36%).

In general, the studies on abuse of buprenorphine or buprenorphine-naloxone observed reductions in reported buprenorphine abuse after marketing started for buprenorphine-naloxone. The exception was the study by Bruce et al.

Reference ID: 3292351

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

/s/

JAMES TRINIDAD
04/12/2013

CATHERINE M DORMITZER
04/12/2013

CYNTHIA J KORNEGAY
04/12/2013

ELIZABETH M MALONEY
04/12/2013

JUDY A STAFFA
04/12/2013

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology Review (OSE)

Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Discussion on Postmarketing Data

Date:	April 12, 2013
Reviewers:	James Phillip Trinidad, M.P.H., M.S., Regulatory Review Officer
	Division of Epidemiology II
Team Leader	Elizabeth Maloney, M.S., Dr.P.H., Epidemiology Team Leader
	Division of Epidemiology II
Division Director	Judy Staffa, Ph.D., R.Ph., Director
	Division of Epidemiology II
Drug Name:	OxyContin®
Subject	Discussion on Postmarketing Data for Reformulated OxyContin®
Application Type/Number:	NDA 22-272; IND 29-038
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2012-1664

TABLE OF CONTENTS

EXECUTIVE SUMMARY 2
1 INTRODUCTION 3
1.1 Background 3
1.2 Regulatory History 4
2 REVIEW METHODS AND MATERIALS 4
2.1 Documents Reviewed 4
3 Discussion 5
3.1 Epidemiological Data 6
3.2 Purdue's Characterizations of Epidemiological Data 20
4 CONCLUSION 21
5 REFERENCES 22

EXECUTIVE SUMMARY

Upon review of postmarketing data submitted by Purdue for reformulated OxyContin®, the Division of Epidemiology II discusses herein the postmarketing data reviewed. This review addresses from a public health standpoint certain postmarketing data presented in a Citizen Petition submitted by Purdue,[1] as well as an interim report submitted by Purdue dated July 30, 2012.

At first glance, preliminary findings from several of the investigations in Purdue's postmarketing study program seem to suggest reductions in abuse of extended-release (ER) oxycodone, including OxyContin®, after the introduction of reformulated OxyContin® to the market. Moreover, analyses comparing prevalence of reformulated OxyContin® abuse to the pre-reformulation prevalence of original OxyContin® abuse suggest a lower prevalence for reformulated OxyContin®. However, the exact interpretation of the above findings becomes unclear when considering that:

- The reductions in ER oxycodone abuse seem to be mostly explained by reductions in other ER oxycodone (such as generic ER oxycodone, not OxyContin®).
- Fewer prescriptions for ER oxycodone and specifically OxyContin® were dispensed after marketing of reformulated OxyContin®, so the reduced availability of ER oxycodone and OxyContin® specifically could explain some of the reductions in abuse.
- Original Oxycontin® and generic ER oxycodone seem to still be abused after the introduction of reformulated OxyContin®, so it is not clear how prevalent reformulated OxyContin® abuse would be in the absence of the availability and abuse of original OxyContin® and generic ER oxycodone.
- Misclassification of the three formulations of ER oxycodone (generic ER oxycodone, original OxyContin®, and reformulated OxyContin®) could occur, and the direction of misclassification could be differential or non-differential, possibly explaining the observed persistence of abuse of original OxyContin® and/or the reductions in OxyContin® abuse.

Findings from the strongest investigation in Purdue's postmarketing study program (the NAVIPPRO™ Investigation of persons entering substance abuse treatment centers) suggests that abuse of reformulated OxyContin® is more oral, and less non-oral, than abuse of original OxyContin®; furthermore, the NAVIPPRO™ data suggest that there were decreases in non-oral abuse of OxyContin® regardless of formulation after marketing started for reformulated OxyContin®. In contrast, the Client Treatment Study Investigation, which was independently conducted by Research Triangle Institute, funded by (b) (4), and also assessed persons entering substance abuse treatment centers, found increases in OxyContin® abuse, including non-oral OxyContin® abuse, after marketing started for reformulated OxyContin®. Exactly why the NAVIPPRO™ Investigation and

[1] Document 0001 of docket ID FDA-2012-P-0760, filed by Kleinfeld, Kaplan and Becker, LLP on behalf of Purdue Pharma L.P.

Reference ID: 3292408

the CTS Investigation yielded divergent results while using similar study designs and methods is currently unknown.

All findings from the postmarketing data bear the following qualifications:

- The prevalence (overall or route-specific) of reformulated OxyContin® abuse could be higher or lower in the absence of the availability and abuse of original formulations of ER oxycodone.
- In the absence of the availability and abuse of original formulations of ER oxycodone, the route-of-abuse profile for reformulated OxyContin® could be more or less non-oral than is currently observed.
- The NAVIPPRO™ Investigation findings need to be appropriately adjusted with a measure of drug utilization and need longer follow-up
- Purdue has not provided any robust data on the clinical outcomes of overdose, poisoning, and death, and the clinical outcome of addiction has not been formally assessed.

Therefore, the Division thinks that the following characterization by Purdue regarding the epidemiological data is stated too strongly:

> "Collectively, these data from ongoing studies demonstrate that reformulated OxyContin is having the effect Purdue intended... These data show that the introduction of reformulated OxyContin has resulted in a decrease in misuse and abuse of OxyContin, and their consequences."

Rather, these data from ongoing studies suggest that reformulated OxyContin may have the effect Purdue intended; and that these data are consistent with the hypothesis that the introduction of reformulated OxyContin could reduce non-oral misuse and abuse of OxyContin.

Furthermore, the Division concludes that Purdue's characterization of *in vivo* and *in vitro* testing providing predictive value for real-world abuse is <u>not</u> supported because the findings from postmarketing investigations of real-world abuse are not robust, and no formal analysis has been conducted characterizing the robustness of a link between *in vitro* experiments and real-world abuse.

Additional follow-up and completion of Purdue's proposed data collection and analyses are needed to definitively evaluate the effect of the reformulation of OxyContin® on OxyContin® abuse and misuse.

1 INTRODUCTION

1.1 BACKGROUND

Upon review of postmarketing data submitted by Purdue for reformulated OxyContin®, the Division of Epidemiology II discusses herein the postmarketing data reviewed. The discussion includes the Division's opinion on Purdue's characterization of the current postmarketing data, possible relationship between *in vitro* experiments and real-world

Reference ID: 3292408

abuse, the Division's characterization of all available data (including postmarketing data and *in vivo* and *in vitro* experiments).

1.2 REGULATORY HISTORY

Reformulated OxyContin® is a single entity extended-release (ER) opioid developed by Purdue Pharma L.P., approved on April 5, 2010, and marketed since August 9, 2010. It has the same indication as the original OxyContin® formulation, which was approved on December 12, 1995. Reformulated OxyContin® is indicated for "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." Compared to the original formulation, reformulated OxyContin® is more resistant to tampering, specifically, dissolving in liquids, breaking, crushing, or chewing.

Purdue hypothesized that the reformulation of OxyContin® would reduce abuse via injection and snorting, and possibly via oral routes that involve breaking, crushing, or chewing. In the New Drug Application Approval Letter dated April 5, 2010, FDA stipulated a postmarketing requirement that Purdue assess "the known serious risks of [reformulated OxyContin®], in particular, whether the changes made to [OxyContin®] that are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences…addiction, overdose, and death."

In July 2012, Purdue submitted an interim report, which describes preliminary findings for eleven investigations that collectively aim to assess the effects of the reformulation of OxyContin® on OxyContin® abuse. In February 2013, FDA received a final report prepared by Research Triangle Institute, containing two additional investigations of postmarketing data on OxyContin®, separate from Purdue's postmarketing study program.

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS REVIEWED

The basis for the Division of Epidemiology II's discussion (see Section 3) includes Purdue Pharma's characterization of the postmarketing data, reviews of data submitted for Purdue's postmarketing study program, two previous reviews of Purdue's postmarketing study program, and an addendum to the July 2012 interim report review (1-5):

- Mathers, P. R. & Davidson, J. A. (2012). Citizen Petition. Kleinfeld, Kaplan, and Becker, L.L.P. *on behalf of* Purdue Pharma, L.P. Submitted to FDA on Jul 18, 2012, for NDA #022272: SDN 167 / eCTD 0140.
- Purdue Pharma L.P. (2012). 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. Submitted to FDA on Jul 31, 2012, for NDA #022272: SDN 171 / eCTD 0143.

Reference ID: 3292408

- Trinidad, J. & Dormitzer, C. (2012). Review of "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011)". FDA/CDER/OSE. Submitted to DARRTS on Apr 27, 2012, for NDA #022272.
- Trinidad, J., Dormitzer, C., & Kornegay, C. (2013). Review of "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". FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.
- Trinidad, J. (2013). Addendum to Review of "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" – Client Treatment Study, National Survey on Drug Use and Health, National Poison Data System, and ARGUS. FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.

3 DISCUSSION

Evaluating changes in route-specific abuse is the broad primary objective of Purdue's study program because the reformulation of OxyContin® is hypothesized to directly affect risk of abuse via non-oral routes of administration. The other two broad objectives were to evaluate changes in overall - rather than route-specific – abuse and to evaluate changes in societal, economic, and behavioral aspects of abuse.

The Division of Epidemiology II thinks that three of Purdue's eleven investigations, when modified and completed, will enable a more complete evaluation of whether marketing the reformulation of OxyContin® subsequently affected the prevalence of overall abuse and misuse of OxyContin®, and the prevalence of route-specific abuse. These investigations are formal studies of abuse that use the following data sources:

- Addiction Severity Indicator – Multimedia Version (ASI-MV®) and Comprehensive Health Assessment for Teens (CHAT™), components of the National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™)
- Research Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program (SPCP)
- National Poison Data System (NPDS)

The other eight investigations could provide the above three investigations with additional context on societal, behavioral, and clinical aspects of OxyContin® abuse.

Only the NAVIPPRO™ Investigation in Purdue's interim report had interim findings for route-specific abuse. The Client Treatment Study (CTS) Investigation, which was one of

Reference ID: 3292408

two investigations conducted by the Research Triangle Institute, also had findings for route-specific abuse.

A separate review of the July 2012 interim report, and a corresponding addendum, contains a thorough discussion of the methods and findings of the thirteen investigations, and serves as the basis for this discussion by the Division of Epidemiology II.

3.1 EPIDEMIOLOGICAL DATA

Overview of currently available epidemiological data

At first glance, preliminary findings from several of the investigations in Purdue's postmarketing study program seem to suggest reductions in abuse of extended-release (ER) oxycodone, including OxyContin®, after the introduction of reformulated OxyContin® to the market. Moreover, analyses comparing prevalence of reformulated OxyContin® abuse to the pre-reformulation prevalence of original OxyContin® abuse suggest a lower prevalence for reformulated OxyContin®. However, these findings do not provide definitive evidence of abuse-deterrence as methodological limitations make the exact interpretation of the findings unclear. Even so, the Division noted that any decrease in OxyContin® abuse following the introduction of reformulated OxyContin® was mainly limited to non-oral routes of administration, as suggested by the NAVIPPRO™ Investigation. On the other hand, the Client Treatment Study (CTS) Investigation, which Research Triangle Institute (RTI) conducted independently from Purdue's postmarketing study program, actually suggests an increase in OxyContin® abuse.

Detailed summary of currently available epidemiological data

The NAVIPPRO™ Investigation and the CTS Investigation both assess overall (that is, not route-specific) and route-specific OxyContin® abuse among a population of clients entering substance abuse treatment, but yielded divergent results.

Of all the investigations in Purdue's postmarketing study program, the NAVIPPRO™ Investigation has the strongest study design because it addresses <u>most, but not all,</u> of the study characteristics needed to assess the effect of the reformulation on OxyContin® abuse and misuse. Specifically, the NAVIPPRO™ Investigation had the following study characteristics:

- a direct assessment of OxyContin® abuse
- focus on a population at-risk of OxyContin® abuse
- stratification of abuse by routes of administration
- stratification of OxyContin® abuse by formulation
- an indirect examination of addiction[2]
- an assessment of the level and trend for various measures of OxyContin® abuse

[2] The NAVIPPRO™ Investigation indirectly assessed addiction since the study population included individuals who entered substance abuse treatment and were likely addicted to the substances they abused.

Reference ID: 3292408

The NAVIPPRO™ Investigation did not do the following:

- appropriately account for availability of OxyContin® (for example, appropriately calculate rates of OxyContin® abuse per OxyContin® tablets dispensed)
- directly assess OxyContin® misuse, which other investigations do assess
- examine overdoses, poisonings, and deaths associated with OxyContin®, which other investigations intend to examine
- address how the OxyContin® risk evaluation and mitigation strategy (REMS), which was instituted specifically for reformulated OxyContin®, may have affected OxyContin® abuse and misuse

The NAVIPPRO™ Investigation found that, compared to abuse of original OxyContin® before marketing started for reformulated OxyContin®, abuse of reformulated OxyContin® was statistically significantly lower in terms of:

- overall (that is, not route-specific) prevalence of abuse
- prevalence of abuse via any oral route of administration
- prevalence of abuse via non-oral routes of administration (all, injection, smoking, and snorting)
- percent of adults abusing OxyContin® via non-oral routes of administration
- number of days of abuse in the past 30 days

The NAVIPPRO™ Investigation found that, among all adults entering substance abuse treatment and who reported prescription opioid abuse, the prevalence of overall (that is, not route-specific) abuse of reformulated OxyContin® (12.1%) was 49% lower than the prevalence of overall abuse of original OxyContin® before marketing started for reformulated OxyContin® (b) (4)), a statistically significant finding (Figure 1a). The relative percent difference among all adults entering substance abuse treatment was similar ((b) (4) with the prevalence of reformulated OxyContin® abuse being (b) (4) and the prevalence of original OxyContin® abuse before marketing of reformulated OxyContin® being (b) (4)

Among adults who reported prescription opioid abuse, there was a (b) (4) relative percent decrease in the prevalence of oral abuse of reformulated OxyContin® compared to oral abuse of original OxyContin® (Figure 1b), a statistically significant finding. More importantly, there was a (b) (4) relative percent decrease in the prevalence of non-oral abuse of reformulated OxyContin® compared to non-oral abuse of original OxyContin® before marketing started for reformulated OxyContin® (Figure 1c), also a statistically significant finding.

Reference ID: 3292408

Figure 1a: Prevalence of abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Figure 1b: Prevalence of oral abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Reference ID: 3292408

Figure 1c: Prevalence of non-oral abuse of various categories of extended-release (ER) oxycodone, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data in Figure 1a-c does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Note: The comparison performed in the interim report was between the prevalence of original OxyContin® before marketing started for reformulated OxyContin® versus prevalence of abuse of reformulated OxyContin®.

Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified.

Purdue concluded that this investigation found substantially lower abuse rates for reformulated OxyContin® than for historical abuse of original OxyContin®.

However, it is unknown whether Purdue's conclusion will be robust after these results are adjusted for availability of each formulation and study follow-up is extended.

More importantly, the Division of Epidemiology II finds that Purdue's conclusion requires qualification with regard to the persistence of original OxyContin® abuse after marketing started for reformulated OxyContin® (Figure 2) [3], a persistence of abuse also observed in the RADARS® SPCP Investigation. The inherent assumption in the NAVIPPRO™ Investigation's (and other investigation's) pre-post analyses of OxyContin® abuse is that, following the introduction of reformulated OxyContin® to the market, brand and generic original formulations of ER oxycodone were not available for abuse after a reasonable transition period. Even though commercial distribution of these

[3]Data on other ER oxycodone abuse each quarter-year after the introduction of reformulated OxyContin® was not presented, so there is not sufficient information to determine whether abuse of other ER oxycodone also persisting. In this context, other ER oxycodone refers to generic ER oxycodone, OxyContin® from Canada or Mexico, and other ER oxycodone not otherwise specified.

Reference ID: 3292408

products ended, abuse of brand and generic original formulations of ER oxycodone continued after reformulated OxyContin® was marketed. Because the assumption stated above was violated, the prevalence of reformulated OxyContin® abuse estimated in the NAVIPPRO™ Investigation could be a systematic underestimation of the possible prevalence of reformulated OxyContin® abuse in the absence of the availability and abuse of brand and generic original ER oxycodone.

There are several possible explanations for continued abuse of original ER oxycodone, including misclassification of reformulated OxyContin® abuse as original ER oxycodone abuse. Since original OxyContin® and generic ER oxycodone seem to still be abused after the introduction of reformulated OxyContin®, it is not clear how prevalent reformulated OxyContin® abuse would be in the absence of the availability and abuse of original OxyContin® and generic ER oxycodone.

Figure 2: Prevalence of abuse of specific opioids‡ among adults† who entered substance abuse treatment from the third quarter of 2009 (3Q2009) to the first quarter of 2012 (1Q2012): An illustration of the persistence in original OxyContin® abuse (in the red box)

(b) (4)

Data Source: Purdue's response to FDA's Information Request, dated Sep 10, 2012, specifically, the worksheet "Figure 9" in the workbook NAVIPPRO System.xls.

†Clients admitted into substance abuse treatment more than once are counted multiple times. Purdue modeled the prevalences shown here with GEE modeling to account for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Marketing started for reformulated OxyContin® in Aug 9, 2010, which is in 3Q2010.

The persistence in original OxyContin® abuse contributed to a persistence in abuse of OxyContin® regardless of formulation. After delineating ER oxycodone by country of origin and formulation, abuse of brand name U.S. ER oxycodone (OxyContin®) statistically significantly decreased after reformulated OxyContin® was marketed, but only by (b) (4) relative to before reformulated OxyContin® was marketed (Figure 1a and Table 1).

Reference ID: 3292408

Thus, although the Division observed that there was a statistically significant reduction in the prevalence of ER oxycodone abuse and OxyContin® abuse (Figure 1a, Table 1), this reduction seem to be mostly explained by reductions in abuse of 'other ER oxycodone,' rather than in abuse of 'brand name U.S. ER oxycodone' (OxyContin®). Other ER oxycodone encompasses generic ER oxycodone, OxyContin® from Canada and Mexico, and OxyContin® whose formulation and country of origin was not otherwise stated.

Reductions in the availability of the various ER oxycodone formulations could also have contributed to the reductions in abuse of ER oxycodone, OxyContin®, and generic ER oxycodone. Indeed, fewer prescriptions for ER oxycodone and specifically OxyContin® were dispensed after marketing of reformulated Oxycontin®. Furthermore, the Division of Epidemiology II noted that the reductions in abuse of 'other ER oxycodone' (Figure 1a, Table 1) were consistent with the reductions in prescriptions dispensed for generic ER oxycodone after marketing started for reformulated OxyContin®.

Reference ID: 3292408

Table 1: Prevalence of abuse of various categories of OxyContin® extended-release (ER) oxycodone abuse, among adults† who entered substance abuse treatment and reported prescription opioid abuse, before (June 1, 2009, to August 8, 2010) and after‡ (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by route of administration

(b) (4)

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

†Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

‡Reformulated OxyContin® was not marketed before Aug 9, 2010.

Other ER oxycodone (that is, not brand-name U.S. ER oxycodone) includes generic ER oxycodone, OxyContin® from Canada and Mexico, and OxyContin® whose formulation and country of origin was not otherwise stated

*Statistically significant at p-value < 0.05

Misclassification of the three formulations of ER oxycodone (generic ER oxycodone, original OxyContin®, and reformulated OxyContin®) could occur, and the direction of misclassification could be differential or non-differential, possibly explaining the observed persistence of abuse of original OxyContin® and/or the reductions in OxyContin® abuse. With regard to reductions in OxyContin® abuse, misclassification of generic ER oxycodone abuse as OxyContin® abuse could happen since OxyContin® is the recognizable brand name of the generic formulations. If this misclassification were to occur, and since prevalence of generic ER oxycodone abuse substantially declined

Reference ID: 3292408

after marketing of reformulated OxyContin®, then reductions in OxyContin® abuse could simply reflect reductions in abuse of misclassified generic ER oxycodone. Since no validation studies have been conducted with NAVIPPRO™ data to examine and quantify potential misclassification among ER oxycodone formulations, whether misclassification is affecting the NAVIPPRO™ Investigation's findings in this manner cannot be assessed.

Misclassification of abuse of reformulated OxyContin® reported as abuse of original OxyContin® could be one of many possible explanations for the persistence in original OxyContin® abuse, but misclassification is not likely the sole explanation for this persistence. Analyses conducted in response to FDA's information requests suggest that misclassification may be present, since the route of administration profile of original OxyContin® abuse seemed to shift from a mainly non-oral abuse profile toward a more oral abuse profile, which is the route of administration profile observed for reformulated OxyContin® (Figure 3a and Figure 3b). There was not a complete convergence of these profiles, so misclassification does not likely entirely explain the persistence in original OxyContin® abuse.

Figure 3a: Percent of adults[α] who reported abuse via oral and non-oral routes of administration, among those who abused original OxyContin®, before (3Q2009-2Q2010) and after (3Q2010-3Q2012) marketing started for reformulated OxyContin®: An illustration of a possible shift away from non-oral and toward oral abuse of original OxyContin®

(b) (4)

Reference ID: 3292408

Figure 3b: Percent of adults[α] who reported abuse via oral and non-oral routes of administration, among those who abused reformulated OxyContin®, after (3Q2010-3Q2012) marketing started for reformulated OxyContin®: An illustration that reformulated OxyContin® abuse is primarily via oral routes of administration

(b) (4)

[†]The figures include data from Jun 1, 2009, which is in 3Q2009, through Sep 30, 2012, which is in 3Q2012.

[‡]Marketing started for reformulated OxyContin® on Aug 9, 2010, which is in 3Q2010.

[α]Clients admitted into substance abuse treatment more than once are counted multiple times. The data presented here does not adjust for potential clustering of abuse patterns for clients admitted into substance abuse treatment more than once.

Note: The sum of the percent of all the routes of administration per OxyContin® formulation is greater than 100% because adults may report abuse of each opioid via several routes of administration.

Data source: Purdue's response to FDA's Information Request, dated Dec 20, 2012

In a response to an FDA request regarding the postmarketing data submitted in the July 2012 interim report, Purdue noted that the route of administration profile for abuse of ER oxycodone remained relatively unchanged after marketing started for reformulated OxyContin® (Figure 4a-e). Purdue also noted that reformulated OxyContin® was less likely to be abused through non-oral routes of administration than the other ER oxycodone categories assessed. In turn, the NAVIPPRO™ data suggest that there were decreases in non-oral abuse of OxyContin® regardless of formulation after marketing started for reformulated OxyContin®.

The Division of Epidemiology II agrees in part with Purdue's observation in that reformulated OxyContin® does appear to be abused less via non-oral routes of administration than original OxyContin® and other ER oxycodone. However, the Division also noted that the route of administration profile for reformulated OxyContin® cannot be fully assessed at this time given the persistent abuse of original OxyContin® and other ER oxycodone. That is, it cannot be determined at this time whether clients of

Reference ID: 3292408

substance abuse treatment will abuse reformulated OxyContin® more via non-oral routes of administration after they have exhausted all licit and illicit supplies of original OxyContin®.

Figure 4a: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

Reference ID: 3292408

Figure 4b: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported non-oral abuse of ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Figure 4c: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported injecting ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Reference ID: 3292408

Figure 4d: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported smoking ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

(b) (4)

Figure 4e: Percent of adults† who, upon stating that they abused extended-release (ER) oxycodone, reported snorting ER oxycodone, before (June 1, 2009, to August 8, 2010) and after (August 9, 2010, to March 31, 2012) marketing started for reformulated OxyContin®, by ER oxycodone category

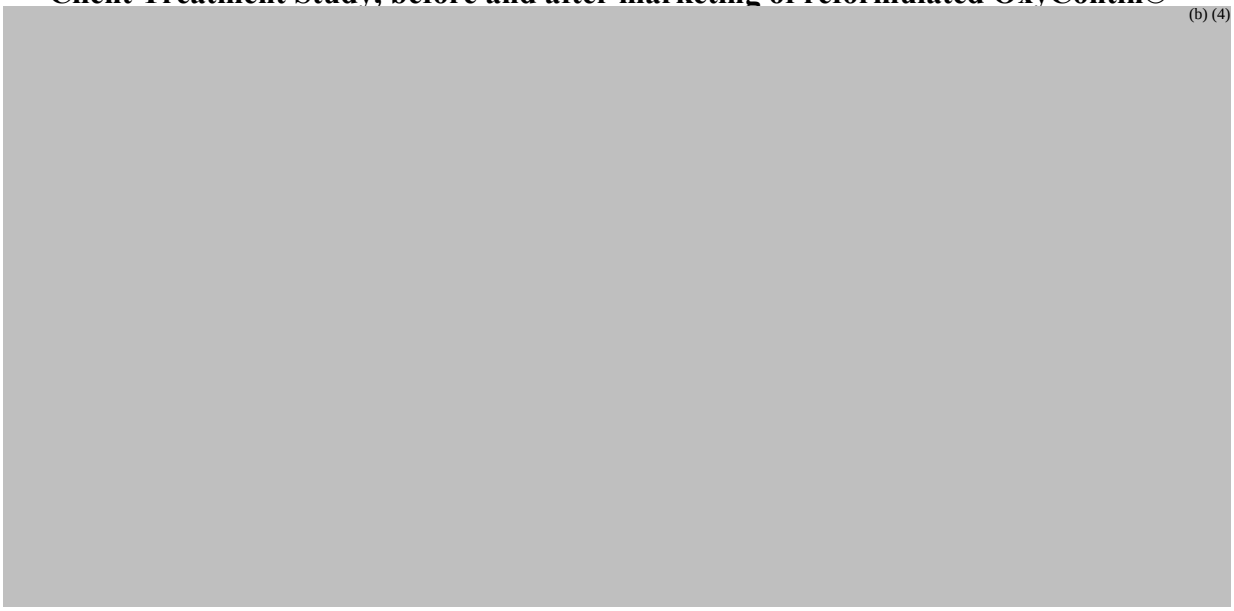
(b) (4)

Reference ID: 3292408

Contrary to findings in the NAVIPPRO™ Investigation, the CTS Investigation found statistically significant increases in the prevalence of OxyContin® abuse (Figure 5) and in the percent of clients who reported usually abusing OxyContin® non-orally (Figure 6), after marketing of reformulated OxyContin®. Specifically, the prevalence of OxyContin® abuse increased from 2.6% of clients one year before marketing started for reformulated OxyContin® to 2.9% of clients one year afterward. Similarly, the percent of clients who reported usually abusing OxyContin® non-orally was 44% one year before marketing started and 48% afterwards.

Figure 5a: Prevalence of past 30-day OxyContin® abuse among clients entering the Client Treatment Study, before and after marketing of reformulated OxyContin®

(b) (4)



Data source: Figures 12 and 13 of RTI's final study report "Surveillance of OxyContin Abuse: A Time Series Analyses of Nonmedical Use, Abuse, and Tampering Patterns Before and After the Reformulation of OxyContin"

Reference ID: 3292408

Figure 6: Percent of Client Treatment Study clients who reported non-oral usual routes of administration if abusing OxyContin®, before and after marketing of reformulated OxyContin®

(b) (4)

Data source: Figure 4 of RTI's final study report "Surveillance of OxyContin Abuse: A Time Series Analyses of Nonmedical Use, Abuse, and Tampering Patterns Before and After the Reformulation of OxyContin"

Exactly why the NAVIPPRO™ Investigation and the CTS Investigation yield divergent results when using similar study designs and methods is not currently known. One explanation may be that these investigations are generalizable to two different populations (for example, the NAVIPPRO™ clients may be more advanced in their addictions and more likely to be using OxyContin® through non-oral routes). It is also possible that the CTS Investigation's study timeframe is too short to observe a true effect of the reformulation on OxyContin® abuse. These explanations are speculative and require additional years of follow-up data (for both investigations) and further data on the characteristics of the study populations and treatment centers providing data.

Purdue's postmarketing study program to date has presented no robust data on changes in the clinical outcomes of abuse and misuse related to the marketing of reformulated OxyContin. In particular, assessments of overdoses and poisonings as well as mortality, all of which are an integral part of the postmarketing requirement, were missing from the three formal studies of Purdue's interim report.

In summary, the Division noted that any decrease in abuse of OxyContin® following the introduction of reformulated OxyContin® is mainly limited to non-oral routes of administration. Specifically, the NAVIPPRO™ Investigation found that reformulated OxyContin® abuse had a primarily oral route of administration profile, in contrast to the primarily non-oral route of administration profile for original OxyContin®.

Reference ID: 3292408

3.2 PURDUE'S CHARACTERIZATIONS OF EPIDEMIOLOGICAL DATA

In light of the discussion above, the Division thinks that the following characterization by Purdue regarding the epidemiological data is stated too strongly:

> "Collectively, these data from ongoing studies demonstrate that reformulated OxyContin is having the effect Purdue intended... These data show that the introduction of reformulated OxyContin has resulted in a decrease in misuse and abuse of OxyContin, and their consequences."

Rather, these data from ongoing studies suggest that reformulated OxyContin may have the effect Purdue intended; and that these data are consistent with the hypothesis that the introduction of reformulated OxyContin could reduce non-oral misuse and abuse of OxyContin.

In addition:

1. The prevalence (overall or route-specific) of reformulated OxyContin® abuse could be higher or lower in the absence of the availability and abuse of original formulations of ER oxycodone.
2. In the absence of the availability and abuse of original formulations of ER oxycodone, the route-of-abuse profile for reformulated OxyContin® could be more or less non-oral than is currently observed.
3. The NAVIPPRO™ Investigation findings need to be appropriately adjusted with a measure of drug utilization and needs longer follow-up.
4. Purdue has not provided any robust data on the clinical outcomes of overdose, poisoning, and death, and the clinical outcome of addiction has not been formally assessed.
5. Although the NAVIPPRO™ Investigation found statistically significant decreases in non-oral abuse, the CTS Investigation found statistically significant increases in non-oral abuse.

Purdue also characterized a link between the *in vitro* experiments Purdue conducted and real-world abuse. This characterization contains two elements:

1. "These epidemiologic studies show significant reductions in exactly those types of abuse and misuse that reformulated OxyContin was anticipated to affect based on the results of the comprehensive battery of *in vitro* studies conducted prior to approval of NDA # 22-272.
2. [These reductions indicate that] Purdue's *in vitro* experiments have predictive value."

<u>The Division of Epidemiology II agrees in part with the first element of Purdue's characterization in that findings on non-oral real world abuse seem to be consistent with what could be expected from *in vitro* experiments.</u> Specifically, the preliminary NAVIPPRO™ Investigation findings suggest that the primarily oral route of

Reference ID: 3292408

administration profile for reformulated OxyContin® was different than the primarily non-oral profile for original OxyContin®, consistent with Purdue's hypothesis.

However, having a real-world finding consistent with what could be expected from the *in vitro* experiments does not make the experiments 'predictive' in epidemiological parlance. A predictive link would require:

1. robust findings from *in vitro* experiments
2. robust findings from postmarketing investigations of real-world abuse
3. a robust link between the experiments and investigations

Because of methodological limitations (see above), the Division cannot conclude that Purdue's investigations found robust reductions in non-oral abuse. Indeed, the current preliminary findings are simply suggestive of reductions in non-oral abuse, a finding supported mainly by the NAVIPPRO™ Investigation, but was not supported by the CTS Investigation.

In epidemiologic terms, predictive value may be determined by conducting specific analyses designed to assess that the *in vitro* experiments predict postmarketing results, thereby addressing the third requirement. At this time, Purdue has not conducted these analyses. Furthermore, because findings on non-oral abuse are supported mainly from one investigation (the NAVIPPRO™ Investigation) and not supported by another (the CTS Investigation), there is no consistency at this time among the postmarketing investigations to corroborate a robust link.

For the above reasons, the Division finds that whether *in vitro* experiments have predictive value for real-world abuse cannot be determined at this time.

4 CONCLUSION

In summary, the Division of Epidemiology II noted that preliminary findings from several of the investigations in Purdue's postmarketing study program are suggestive of reductions in OxyContin® abuse after the introduction of reformulated OxyContin® to the market, but these findings do not provide definitive evidence of abuse deterrence as methodological limitations make the exact interpretation of the findings unclear. In addition, the Division noted that any decrease in OxyContin® abuse following the introduction of reformulated OxyContin® was mainly limited to non-oral routes of administration.

In contrast to the strongest investigation in Purdue's postmarketing study program (the NAVIPPRO™ Investigation), the CTS Investigation, which was conducted by Research Triangle Institute, found increases in OxyContin® abuse, including non-oral abuse after marketing of reformulated OxyContin® began. Exactly why the NAVIPPRO™ Investigation and the CTS Investigation yielded divergent results while using similar methods is currently unknown.

All findings from these investigations bear qualification as the data are too premature to draw conclusions:

Reference ID: 3292408

- The prevalence (overall or route-specific) of reformulated OxyContin® abuse could be higher or lower in the absence of the availability and abuse of original formulations of ER oxycodone.
- In the absence of the availability and abuse of original formulations of ER oxycodone, the route-of-abuse profile for reformulated OxyContin® could be more or less non-oral than is currently observed.
- The NAVIPPRO™ Investigation findings need to be appropriately adjusted with a measure of drug utilization and needs longer follow-up
- Purdue has not provided any robust data on the clinical outcomes of overdose, poisoning, and death, and the clinical outcome of addiction has not been formally assessed.

In particular, longer follow-up is needed for Purdue's postmarketing study program to evaluate the persistence of original OxyContin® abuse, and also to allow Purdue to complete planned assessments and analyses of clinical outcomes.

For these reasons, the Division finds that Purdue's characterization - that there are decreases in abuse, misuse, and subsequent clinical outcomes after the introduction of the reformulation of OxyContin® - is stated too strongly. The Division's determination is that these findings are suggestive, and not definitive at this time.

It is not in the purview of the Division of Epidemiology II to comment on the methods and findings of the *in vivo* and *in vitro* test and experiments. Still, upon reviewing the interim report for Purdue's postmarketing study program, the Division concludes that whether *in vivo* and *in vitro* testing and experiments are predictive of real-world abuse cannot be determined at this time because the postmarketing investigations of real-world abuse are not robust, and no formal analysis has been conducted characterizing the robustness of a link between *in vitro* experiments and real-world abuse.

5 REFERENCES

1. Mathers, P. R. & Davidson, J. A. (2012). Citizen Petition. Kleinfeld, Kaplan, and Becker, L.L.P. *on behalf of* Purdue Pharma, L.P. Submitted to FDA on Jul 18, 2012, for NDA #022272: SDN 167 / eCTD 0140.

2. Purdue Pharma L.P. (2012). 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. Submitted to FDA on Jul 31, 2012, for NDA #022272: SDN 171 / eCTD 0143.

3. Trinidad, J. & Dormitzer, C. (2012). Review of "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences:

Reference ID: 3292408

Addiction, Overdose and Death (as of October 15, 2011)". FDA/CDER/OSE. Submitted to DARRTS on Apr 27, 2012, for NDA #022272.

4. Trinidad, J., Dormitzer, C., & Kornegay, C. (2013). Review of "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". FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.

5. Trinidad, J. (2013). Addendum to Review of "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" – Client Treatment Study, National Survey on Drug Use and Health, National Poison Data System, and ARGUS. FDA/CDER/OSE. Submitted to DARRTS on Apr 12, 2013, for NDA #022272 and IND #029038.

Reference ID: 3292408

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

/s/

JAMES TRINIDAD
04/12/2013

ELIZABETH M MALONEY
04/12/2013

JUDY A STAFFA
04/12/2013

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 11, 2013

To: Douglas Throckmorton, M.D., Deputy Director
Center for Drug Evaluation and Research, FDA

From: Michael Klein, Ph.D., Director
Controlled Substance Staff

Subject: Study of Abuse Deterrence Characteristics of Reformulated OxyContin Relative to Original OxyContin
Sponsor: Purdue Pharma L.P.

Background

On October 3, 2008, the Agency issued a Complete Response letter to Purdue Pharma L.P., regarding its proposed reformulation of OxyContin, under NDA 22-272, which was developed to be abuse deterrent. The Agency requested additional testing of the reformulated tablets to demonstrate the new properties of the OxyContin tablets. Subsequently, Purdue submitted several studies that were intended to demonstrate that the physical properties of the product's formulation are more difficult to abuse by non-oral routes. The Purdue studies are summarized in a publication in *Drug and Alcohol Dependence* (Cone, E.J., et al., An interative model for in vitro laboratory assessment of tamper deterrent formulations. Drug Alcohol Depend. (2013), http://dx.doi.org/10.1016/J.drugalcdep.2012.12.006).

The goal of abuse deterrent product development is to formulate finished dosage forms to make them difficult to tamper (e.g., destroy the controlled release mechanism to obtain pure drug for abuse), or to make them not rewarding after being tampered. The formulation is expected to be more difficult to crush or extract the active pharmaceutical ingredient (API) in a pure form. Also, the formulation may impede diversion of multiple immediate release (IR) doses of oxycodone, the active pharmaceutical ingredient (API), derived from the tampered extended release long acting (ER/LA) tablet, and thus be a safer product both for the legitimate patients as well as opioid drug abusers.

Conclusion

The CSS evaluation of new drug products for abuse deterrence properties can be accomplished by a premarketing assessment of a wide range of physicochemical studies,

including an appropriately detailed in vitro data package (as described in the paper by E.J.Cone et al. 2013), and clinical study data including a modified, well-designed human abuse potential (liability) study and comparative pharmacokinetics and pharmacodynamic study of intact and manipulated products, relative to appropriate positive controls. CSS relied upon the scientific reviews of Dr. James Tolliver on the in vitro studies that tested the physicochemical properties of reformulated OxyContin (OCR reviewed in 2009) and clinical study results (reviewed in 2012). In addition, CSS relied upon the pharmacokinetics review (2012) of Dr. Shrikant Nallani. CSS also relied upon the statistical review (by Dr. Ling Chen 2012) of one of the five clinical studies (OTR1018) which evaluated the abuse potential and pharmacodynamic effects of intranasal administration of the reformulated OxyContin [intact, crushed coarse and fine powders), finely crushed original OxyContin (OC), oxycodone powder and placebo].

The Sponsor provided in vitro chemical and in vivo study data that demonstrated that the reformulated OxyContin (OCR) product had the following improvements over the original OxyContin (OC) product, relative to abuse, misuse, and diversion.

1. Extraction of oxycodone (API) from OCR by common solvents was more difficult (in vitro).
2. Crushing OCR by common methods was made more difficult (in vitro).
3. Injection (intravenous) of extracted API was more difficult, as syringeability was impeded (in vitro).
4. Oral abuse was still possible. However, there was no distinction between oral abuse occurring by swallowing or chewing. The process described as "normal chewing" of OCR was made more difficult (according to in vivo pharmacokinetics). Additionally, the Tmax for OCR when taken according to labeled instructions, was twice as long as the Tmax of OC (OCR median Tmax 4.5 hours vs. OC Tmax 2.5 hours).
5. Intranasal abuse of crushed OCR was made less rewarding as demonstrated by “drug liking” and PK/PD analysis from a human abuse potential study (in vivo human abuse study).
6. Smoking for inhalation of oxycodone as the hydrochloride salt was difficult whether it was obtained from OCR or OC. At high temperatures, the substance decomposes prior to its vaporization (in vitro).

Discussion

In March 2009, the Sponsor provided detailed information on in vitro studies conducted to evaluate the tamper resistant characteristics of the reformulated tablets. In September 2010, the Sponsor provided detailed information on in vivo studies (PK, PD) conducted to evaluate abuse deterrent characteristics of the reformulated tablets. The data are described in the paper by E.J.Cone (*Drug Alcohol Depend*., 2013). Sponsor’s experiments were shown to be replicated to assess imprecision and result in robust datasets. Multiple replicates of each dosage strength for each condition tested produced a collection of thousands of data points for crushing and extraction studies. Results of

Reference ID: 3292186

manipulated product were compared to OC and to intact OCR. Studies included crushing to test particle size reductions using a variety of tools of varying strengths, from spoons to coffee grinders. The particles were separated by sieve analysis into a series of six bands by particle size. Studies were then conducted on each of the six bands, ranging from coarse to fine (b) (4)). Extraction studies included solvents with a wide range in polarities at room temperature and with heat. Time of extraction and degree of fractionation of particles in each band were examined. In vitro dissolution studies of intact tablet and the six particle size bands were conducted in simulated gastric fluid (SGF) and with a mixture of ethanol and SGF, to test for possible "dose dumping" with ethanol use. In addition, syringeability and injectability studies evaluated the feasibility of preparation of an injectable dose of oxycodone; the studies demonstrated that gelling characteristics of OCR made it more difficult to prepare an oxycodone solution for injection than from the original OxyContin product. Vaporization experiments assessed the process of inhalation of the drug by application of heat (smoking). Since the API is the form of the hydrochloride salt of oxycodone (for both OC and OCR), sufficient heat must be applied to drug to vaporize prior to reaching a temperature of decomposition.

The ER/LA formulations containing large amounts of opioids may undergo tampering by crushing or dissolution resulting in the release of large doses of drug. The tampered formulations can then be ingested, snorted, smoked or intravenously administered. The oral route is the most commonly used route for the misuse and abuse of OxyContin. Oral route includes swallowing whole and chewing. More experienced abusers report injecting or inhaling crushed OxyContin tablets. As reflected in the approved labeling, the use of opioid analgesics carries the risk of addiction even under appropriate medical use.

In Vitro Studies

Detailed in vitro testing to characterize tamper resistant properties was conducted on all dosage strengths of reformulated OxyContin (OCR) and compared with the original OxyContin (OC) formulation. The Sponsor conducted an extensive number of in vitro studies in order to characterize the tamper resistant properties of the various dosage strengths of reformulated OxyContin tablets (see article by E. J. Cone 2013, described above). Collectively these studies show:

1. Reformulated OxyContin tablets (OCR) are considerably more difficult to chew or crush compared to the original product. A coffee bean or laboratory grinder is required to produce a small particle size powder. By contrast, using 2 stainless steel spoons or using a mortar and pestle were sufficient to reduce the original product (OC) to a fine powder.
2. The greater difficulty in crushing or chewing reformulated OxyContin (OCR) gives the product an enhanced protective advantage over that of the original OxyContin (OC) with regard to enabling the immediate release of a high dose of oxycodone (dose dumping).
3. Water is effective in extracting oxycodone hydrochloride from crushed reformulated and original OxyContin. In general, the reformulated product is a

Reference ID: 3292186

limited improvement over the original OC regarding water solubility. Crushing the product or increasing water temperature result in increased extraction efficacy of oxycodone HCl. Similarly, other common solvents were more effective in extracting oxycodone from the original product.

4. Water is also effective in extracting oxycodone HCl from intact tablets of reformulated OxyContin. Thus, a simple water extraction procedure can afford clinically significant amounts of oxycodone from high strengths of intact and crushed tablets of both the original and reformulated product. However, virtually all of the oxycodone can be quickly removed from OC which is easily crushed to fine particles. Much less oxycodone can be removed from the OCR product; the band of coarsely crushed particles produces much less oxycodone with water extraction within specified time points.
5. Importantly, from a safety viewpoint, crushed OCR retains some controlled release properties, as opposed to OC which releases (b) (4) of oxycodone in 5 minutes.
6. The polyethylene oxide excipient (PeO) makes it difficult to use the reformulated tablets (OCR) to prepare an aqueous solution suitable for intravenous injection. By contrast, the original OxyContin (OC) could be used to prepare a low volume, potent, and aqueous solution for intravenous use.
7. Neither OC nor OCR product would be predicted to be abused by inhalation, since oxycodone HCl decomposes at a temperature that is close to its vaporization temperature.

Pharmacokinetic Study:

For most CNS drugs, the relation of effect and concentration in different populations of test subjects must be shown. Receptor response "sensitivity" is variable and complexly modulated. In addition, we have little information about degrees of tolerance and its relationship to pharmacokinetics. The subject population in a PK study has a lower level of tolerance to opioids than the subject population in a typical human abuse potential study. Also, confidence limits of concentration to effect are wide. In order to attribute meaning to the rate of rise of drug concentration to effect, we need to explore, for example, "drug liking" Emax and Tmax, which may relate to the abuse potential of the product. If this information is not known, the value of PK as a surrogate for abuse liability assessment may be limited. Tampering (such as, by crushing, dissolution, and extraction) of a dosage form (in a range of doses of ER/LA opioid products) can lead to decreased Tmax and Cmax and produce increased scores of "drug liking" that are similar to those of an IR product (described below). Depending on the dissimilarity of populations studied in the PK and PD studies, this pharmacodynamic measure may not correlate well with pharmacokinetic data alone.

OTR1016: A Randomized, Open Exposure to Single Dose Crossover Study of the Effects of Various Tampering Methods on Oxycodone in Fasting Healthy Subjects.

"Vigorous" chewing of intact, crushed, or pre-softened OCR tablets substantially compromises the CR mechanism, as evidenced by an increase in oxycodone Cmax. The

Reference ID: 3292186

Cmax was equivalent to the Cmax achieved from chewed OxyContin original formulation and IR oxycodone, and by a reduction in Tmax.

The OCR formulation was less susceptible to compromise of oxycodone release than was the OC formulation following "normal" chewing, as evidenced by a 23.6% oxycodone Cmax and an approx. 2-fold longer Tmax. Crushing of OTR with a mortar and pestle did not compromise the controlled release properties.

Examination of plasma levels of oxycodone predicted "drug liking" in a humans that "vigorous" chewing of OCR followed by ingestion can produce significant levels of "drug liking" on the VAS. This applies to intact, crushed, or pre-softened OCR.

Thus, the OTR1016 PK study demonstrated that OCR was less susceptible to oxycodone release than OC following "normal" chewing. "Vigorous" chewing substantially compromises the controlled release mechanism of OCR, as resultant plasma levels of oxycodone were equivalent to those following chewing of OC.

Human Abuse Potential Study OTR1018

The clinical evaluation of abuse deterrence was conducted in the following study:

OTR1018: 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

The study provides evidence that OCR may be less susceptible to IN abuse than the original ER formulation and IR oxycodone. IN administration of finely and coarsely crushed OCR and powdered IR oxycodone resulted in levels of "drug liking" and "high" that were significantly greater than IN placebo. Even the finely crushed band for OCR showed less "drug liking" and "Take drug again" than crushed OC. Finely crushed OC produced similar scores in the VAS measures to oxycodone API. It is important to conduct PK analysis in this population and to show consistency and a correlation with the PD results.

Exploration of nasal irritation from crushed OCR as a possible surrogate measure for assessing deterrence should be considered.

Reference ID: 3292186

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

/s/

MICHAEL KLEIN
04/11/2013

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 21, 2012

To: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: IND 29,038 Sequence 0025 (693) - Oxycodone HCl with cross reference to NDA 22, 272 for OxyContin Controlled-Release Tablets, approved April 5, 2010
Indication: Relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Dosages: 30 Oxycodone HCl Tablets
Sponsor: Purdue Pharma L.P.

Materials reviewed: Clinical Study Report OTR1021 entitled "A Randomized, Single-Blind, 3-Way Crossover Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Crushed Intranasal Oxycodone Tamper Resistant Tablets (OTR) and OxyContin in Healthy Adults. (Module 5.3.1.2)

I. Background

In a letter dated September 16, 2010, Purdue Pharma L.P. submitted under IND 29,038 a final study report for clinical study OTR1021, entitled "A Randomized, Single-Blind, 3-Way Crossover Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Crushed Intranasal Oxycodone Tamper Resistant Tablets (OTR) and OxyContin in Healthy Adults." The application was cross referenced to NDA 22,272 for OxyContin Controlled-Release Tablets approved on April 5, 2010.

Subsequently, the Sponsor submitted Citizen Petition FDA 2012-P-0760 dated July 13, 2012, requesting that FDA require that generics referencing reformulated OxyContin (oxycodone hydrochloride extended release) be shown to perform as well as OxyContin when subjected to known and anticipated forms of tampering for purposes of abuse and misuse. As part of the basis for this petition, the Sponsor documented the result obtained from clinical study OTR1021.

Reference ID: 3192789

In response to the citizen's petition, CSS reviewed clinical study OTR1021. The review and conclusions reached by CSS concerning the study are provided below.

II. Conclusions:

Conclusions regarding clinical study OTR1021 are provided below.

- Statistical analysis by the Sponsor showed that intranasal treatment with 10 mg finely crushed original OxyContin (OC) produced a higher oxycodone Cmax (LS mean 21.7 ng/mL) compared to intranasal administration of 10 mg finely crushed OTR (LS mean of 16.8 ng/mL) or 10 mg coarsely crushed OTR (14.5 ng/mL), without affecting total exposure to oxycodone. This suggests that compared to the original OxyContin formulation, the OTR formulation may be less susceptible to intranasal abuse. Detailed information including particle size information as well as the method used and time involved in crushing each formulation were not provided for the three treatments.

- Based on a comparison of the oxycodone Cmax values observed in this study and clinical study OTR1018, as well as an examination of the "drug liking" scores obtained in clinical study OTR1018, it is probable that intranasal administration of 10 mg OTR, finely crushed or coarsely crushed, or 10 mg finely crushed original OxyContin would not result in sufficient drug liking.

- The intranasal tolerability study indicates that nasal irritation is not going to be a deterrent to the intranasal abuse of the specific treatments given in this study. Endoscopic examination by a qualified ears, nose, and throat specialist revealed evidence of nasal irritation in only 3 of 29 subjects. Subject evaluations using the intranasal tolerability rating scales indicate that symptoms such as "discomfort", "itching", "burning", "pain", "runny nose", and "stuffiness" were at most very mild or mild for the three treatments

III. Review of Clinical Study OTR1021

Study OTR1021 was a randomized, single-blind, single-dose, single-center, 3-treatment, 3-period crossover study in fasted healthy adult subjects. The objective of the study was to compare the PK, tolerability, and safety of finely crushed 10 mg Oxycodone Tamper Resistant (OTR) tablets, coarsely crushed 10 mg Oxycodone Tamper Resistant tablets and finely crushed 10 mg original formulation OxyContin (OC) tablets administered intranasally.

Thirty subjects qualified for the treatment phase of the study with 29 subjects completing the study. One subject dropped out of the study due to nausea. Preference for subject selection was given to individuals who had experience in the recreational use of opioids on at least 5 occasions within the past 12 months. Further preference was given to individuals who reported at least 3 occasions of intranasal opioid drug use within the past 12 months. For entry into the study, subjects were required to pass a naloxone challenge test to demonstrate non-dependence to opioids.

Reference ID: 3192789

During the Treatment Phase, a single dose was administered in each of the 3 study periods. A minimum washout period of at least 48 hours separated dose administrations. Subjects were confined to the study center beginning the day before first treatment and continuing throughout the study. Specific treatments included: Treatment A - Finely Crushed 10 mg OTR (OTRf); Treatment B - Coarsely Crushed 10 mg OTR (OTRc); and Treatment C - Finely Crushed 10 mg originally formulated OxyContin (OCf). Subjects administered treatments to alternating nares according to procedures laid out in a "Pharmacy Manuel" but not described in the study report.

Information was not provided concerning the procedures used to crush OTR tablets and originally formulated OxyContin tablets. Other than noting that the crushed material was either "fine" or "coarse", information, such as particle size distribution, was not provided for the three treatments.

Blood samples for determining PK parameters were taken once pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, and 48 hours post-dose.

PK variables for oxycodone assessed during the study included but were not limited to: maximum observed oxycodone plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration time curve from hour 0 to the last measurable plasma concentration (AUCt); and area under the plasma concentration-time curve extrapolated to infinity (AUCinf).

Least square (LS) means were obtained for Cmax, AUCt, and AUCinf for the treatments. For comparison of treatments, the ratios of test/reference (%) values were calculated and examined for falling within the 80% to 125% confidence range. Specific comparisons were OTRf vs. OCf, OTRc vs. OTRc, and OTRc vs. OCf.

In order to assess tolerability of intranasal administration, 29 subjects were required to complete a set of 6 intranasal tolerability scales, each ranging from 0 ("None") to 10 ("Worst I Can Imagine"). One each of the 6 scales assessed "Discomfort," "Itching," "Burning," "Pain," "Runny Nose," and "Stuffiness." Scales were completed immediately pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours after each dosing. For each scale, a least square mean score was determined for each treatment. For treatment comparisons, differences in LS mean scores along with 90% confidence intervals as well as p-values for treatment differences were determined. Group statistics, but not individual responses to the scales, were provided in the study report.

In addition to the subject assessments of intranasal tolerability, an ear, nose, and throat specialist performed a brief endoscopic examination of the nasal cavity. This procedure was completed pre-dose and as close as possible to 0.5 hours, post-dose and not later than 2 hours post-dosing.

Reference ID: 3192789

Oxycodone Pharmacokinetic Results

Lower oxycodone Cmax values, longer oxycodone Tmax values, and no difference in total drug exposure suggest that that OTR tablets may be less susceptible to intranasal abuse than the originally formulated OxyContin tablets.

The oxycodone Cmax LS means following intranasal treatment with 10 mg OTRf, 10 mg OTRc, and 10 mg OCf were 16.8, 14.5, and 21.7 ng/mL, respectively. The ratio of OTRf LS mean Cmax to OCf LS mean Cmax was 77.6 with confidence interval of (69.27, 87.02), therefore partially outside the 80% to 125% range showing that the treatments were not equivalent. Likewise, the ratio of OTRc LS mean to OCf LS mean was 67.0% with confidence interval of 59.76 to 75.07. This fell entirely outside of the 80% to 125% interval indicating a lack of equivalence between the two treatments. The confidence interval (76.91, 96,78) for the ratio of OTRc LS mean to OTF LS mean (86.3) was not entirely within the 80% to 125% range for equivalence. These data indicate that intranasal administration of 10 mg OCf was associated with higher oxycodone Cmax than that produced following intranasal administration of either 10 mg OTRf or 10 mg OTRc. In addition, the oxycodone Cmax following intranasal 10 mg OTRf tended to be higher than the Cmax achieved following intranasal 10 mg OTRc.

According to the Sponsor, the 90% confidence intervals for oxycodone AUCt and AUCinf were entirely contained within the 80 to 125% range for all treatment comparisons, indicating that all treatments were equivalent. As such, each of the treatments resulted in similar total oxycodone exposure.

The time to reach Cmax was shorter for intranasal administration of OCf [median (min, max) = 1.00 hours (0.250, 2.50 hrs)], compared with, following intranasal treatment, either OTRf [median (min, max) = 2.00 (0.75, 3.50)] or OTRc [median (min, max) = 3.00 (1.00, 8.13)].

No measures of positive subjective effects were determined in this study. However, a comparison of the results of this study to the results (pharmacokinetic and subjective reinforcing effects as measured using the bipolar "Drug Liking" Visual Analog Scale (VAS) obtained in the Purdue sponsored study OTR1018 suggest that the intranasal administration of 10 mg OTRf or 10 mg OTRc which achieved mean (SD) oxycodone Cmax values of 17.1 (3.65) and 15.5 (5.61) ng/mL would have produced little in the way of drug liking. In OTR1018, intranasal administration of 30 mg OTRf and 30 mg OTRc resulted in oxycodone Cmax means 29.4 (7.71) and 29.8 (12.2) ng/mL, while producing mean (SD) Emax scores on the Drug Liking VAS of 69.7 (29.4) and 61.1 (25.8), respectively, indicating limited drug liking at these oxycodone Cmax values. As such, intranasal administration of 10 mg OTR, resulting in Cmax values almost half of that produced by 30 mg OTR insufflation, would be expected to produce little drug liking as evidenced by the bipolar drug liking VAS.

Tolerability of Intranasal Administration

The overall results of the intranasal tolerability study suggest that nasal irritation would not be a deterrent to the intranasal abuse of the three treatments given in this study.

Reference ID: 3192789

With regard to the categories of intranasal "itching", "burning, and "pain", there were no differences between the three treatment groups of 10 mg OTRf, 10 mg OTRc, and 10 mg OCf. The least square mean scores for these three categories among the three treatments were less than 2 indicating a very modest effect (0 = no effect, 10 = as worst as it gets).

Using the "Discomfort" scale, intranasal 10 mg OTRf (LS mean 1.4) produced statistically more discomfort than did treatment with 10 mg OCf (LS mean 0.7). Intranasal treatment with 10 mg OTRc (SL mean 2.0) produced significantly more discomfort than did either OTRf or OCf treatment. However, considering the 0 (no effect) -10 (as worst as it gets) scale, the "discomfort" from any of the treatments could be rated as very mild.

Using the nasal "Stuffiness" scale, intranasal treatment with either 10 mg OTRf or 10 mg OTRc (LS mean scores of 3.3 and 3.7) produced significantly more nasal stuffiness than did intranasal 10 mg OCf (LS mean score 1.0). Again, these scores were on the lower end of the 0 to 10 scale indicating overall a mild level of nasal stuffiness

The one other statistically significant finding was that intranasal 10 mg OTRf produced less "runny noise" (LS mean score 0.5) than did intranasal 10 mg OCf (LS mean score of 1.1). These scores were close to the lower end of the 0 to 10 scale, indicating that the overall effect of "runny nose" was very mild.

Nasal endoscopy revealed the presence of white material in the nasal cavity of most of the 29 subjects. However, only three subjects, two with OTRc treatment and one with OCf treatment, displayed mucosal erythema or swelling.
.

Reference ID: 3192789

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

/s/

JAMES M TOLLIVER
09/21/2012

SILVIA N CALDERON
09/21/2012

MICHAEL KLEIN
09/21/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 21, 2012

To: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substances Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: IND 29,038 Sequence 0025 (693) - Oxycodone HCl with cross reference to NDA 22, 272 for OxyContin Controlled-Release Tablets approved April 5, 2010
Indication: Relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Dosages: 30 Oxycodone HCl Tablets
Sponsor: Purdue Pharma L.P.

Materials reviewed: Clinical Study Report OTR1019 entitled "Relative Attractiveness of Oxycodone TR: Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations" (Module 5.3.1.1)

I. Background

In a letter dated September 16, 2010, Purdue Pharma L.P. submitted under IND 29,038 a final study report for clinical study OTR1019 entitled "Relative Attractiveness of Oxycodone TR: Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations." The application was cross referenced to NDA 22,272 for OxyContin Controlled-Release Tablets approved on April 5, 2010.

Subsequently, the Sponsor submitted Citizen Petition FDA 2012-P-0760 dated July 13, 2012, requesting that FDA require that generics referencing reformulated OxyContin (oxycodone hydrochloride extended release) be shown to perform as well as OxyContin when subjected to known and anticipated forms of tampering for purposes of abuse and misuse. As part of the basis for this petition, the Sponsor documented results obtained from clinical study OTR1019.

In response to the citizen's petition, CSS reviewed clinical study OTR1019. The review and conclusions reached by CSS concerning the study are provided below.

Reference ID: 3192781

II. Conclusions:

Following review of OTR1019, conclusions concerning the study are provided below.

- Study OTR1019 can be divided into two sections. Section 1 required subjects to assess various products, including Oxycodone HCl Tamper Resistant (OTR) Tablets, for attractiveness, value, and tamperability after review of "information cards" containing information on each product. In Section 2 of the study, subjects were given the opportunity to tamper with placebos (formulation minus active ingredient) of OTR tablets and the original formulation of OxyContin tablets using specific tools, after which subjects evaluated the ease and usefulness of those tools for tampering with either product.

- The results of Section 2 provide support that OTR tablets, compared to original OxyContin tablets, are less susceptible to physical manipulation when the tools used include either the hammer, pill crusher, mortar and pestle or an X-Acto knife.

- Section 1 which required subjects to assess various products, including OTR tablets and original OxyContin tablets, for attractiveness, value, and tamperability after receiving information from "information cards" is poorly designed thereby making usefulness of this section of the study questionable.

    - It is not appropriate to simply show study subjects a series of cards having selective information that may, in fact, bias subsequent assessments by the subjects of the products. The information provided on the cards, such as crushability, solubility, drug and potency, dosages, and immediate verses extended release, for the various products would be expected to influence subject assessments in a predictable manner.

    - Along with the cards, samples of placebos for OTR tablets and OxyContin Tablets were provided, but the other products were not provided. This gave a signal that these two products are different from the other products, which could bias subject assessments.

    - It is clear from the drug abuse and tampering profile established for the study subjects that none of the subjects had experience with naltrexone containing products and limited or very little experience with tampering of OxyIR and patch products, respectively. This would make it difficult for subjects to assess these products in relationship to the other products, including OTR tablets.

III. Review of Clinical Study OTR1019

Study OTR1019 was sponsored by Purdue Pharma L.P. and conducted by the independent contract organization, [redacted] (b) (4). Study was conducted at a single sight in Canada. Completion date for this study was July 2009.

Reference ID: 3192781

Subjects were recruited by [redacted] (b) (4), using its volunteer database and print advertisements. Subjects were screened by telephone prior to attending the study session. To be included in the study, subjects were required to meet the following criteria:

- 18 years of age or older (male or female)
- Current or recent recreational (nonmedical) opioid users defined as opioid use on at least 10 occasions within the last year, and at least once in the 12 weeks prior to the study session.
- Provided at least 2 examples of pharmaceutical opioid tampering that they had performed in the last 24 months (e.g. crushing, snorting, chewing, extraction from multi-ingredient products)
- Stated a preference for one of three categories of tampering - crushing, snorting, or chewing

Once accepted into the study, subjects were questioned in detail about past drug abuse history. All 30 subjects had experience in abuse with the original formulation of OxyContin in which 28 subjects had tampered with the product. Over half of the subjects reported abuse and tampering with codeine products, Percocet, Percodan, and Dilaudid. Between 50% and 25% of subjects reported abuse and tampering with MS Contin and OxyIR or oxycodone containing products. Most common routes of drug abuse were snorting (46.5), injection (33.3%), crushed oral (10%), and chewed (6.7%). Tampering methods reported use by 50% or more of the subjects including crushing, removal of coatings or layers, chewing, and dissolving in water to take by mouth. Other tampering methods reported included (% of 30 subjects): heating, boiling or melting (46.7%), Dissolving in water for injection (40.0%), Dissolving in alcohol to take by mouth (26.7%), and Dissolving in another solvent to take by mouth (10.0%).

Study was divided into two main sections. First section was assessment of attractiveness by subjects based on subjects viewing "information cards" on the OTR tablet, OxyContin Tablet and other opioid products. The second section involved subjects attempting to tamper with the OTR product and OxyContin tablets using selected tools.

<u>Section 1. Use of "Information Cards"</u>

Thirty subjects were presented with "information cards" on the products listed below. In the case of OTR tablet and OxyContin tablets, subjects were also given placebo samples along with the cards.

- Oxycodone HCl Tamper Resistant (OTR)Tablets
- Original Formulated OxyContin Tablets
- Oxycodone (immediate release oxycodone) tablet (OxyIR)
- Percocet (oxycodone and acetaminophen) tablet
- Percodan (oxycodone and acetylsalicylic acid) tablet
- Hypothetical oxycodone and naltrexone oral product
- Hypothetical oxycodone transdermal patch.

Each information card contained pictures of the products as well as information regarding active ingredient, street names, doses, drug solubility, potency, physical properties (whether or not product is "crushable"), and release properties.

Reference ID: 3192781

Following each card presentation, subjects were asked to assess the product on the card using:

- 5 Point Opiate Attractiveness Scale
- 7 Point Value of Product Scale
- 7 Point Likelihood to Tamper Scale
- Overall Desirability Ranking.

It is the opinion of this reviewer that Section 1 of this overall study (OTR 1019) is not an appropriate study because of introduction of possible bias in the study. It is not appropriate to simply show study subjects a series of cards having selective information that may, in fact, bias subsequent assessments by the subjects of the products. In addition, providing along with the cards samples of placebos for OTR tablets and OxyContin Tablets, but not for the other products, signals that these two products are different from the other products, which may bias subject assessments. It is also clear from the drug abuse and tampering profile establish for the study subjects that none of the subjects had experience with naltrexone containing products and limited or very little experience with tampering of OxyIR and patch products, respectively.

Restricting the assessment comparisons to that between OxyContin and OTR, it is not surprising that compared to OTR tablets, OxyContin tablets were found to have higher values on the Opioid Attractiveness Scale, the Value Product Scale, and the Likelihood to Tamper Scale. These results suggest that OxyContin, in comparison to OTR tablets, according to the 30 subjects is 1) more attractive as a drug of abuse; 2) is considered to have higher value as a drug of abuse; and 3) is more likely to be tampered with in the course of abuse

Section 2. Manipulation of Product

All thirty subjects were given the opportunity to tamper with the placebos (no active drug present) of OxyContin (OC) and OTR tablets. Subjects were given the choice of using the hammer, X-Acto knife, pill crusher or mortar and pestle.

After tampering with the products, subjects were asked to answer the following three questions:

- Do you think that it is feasible to tamper with this product using this method?
- If this product was available to you, would you use this method of tampering?
- If this product was available to you, would you use another method of tampering?

All subjects who attempted to tamper with OC tablets using a hammer, pill crusher, or mortar and pestle felt that it was feasible to tamper with OC tablets using these tools. Fifteen of 17 subjects felt that an X-Acto knife could be used to tamper with OC tablets. By contrast, 77.8 % using a hammer, 86.7% using a pill crusher, 87.5% using a mortar and pestle and 40.9% using an X-Acto knife did not think these methods were feasible for use in tampering with OTR tablets.

The majority of subjects (ranging from 75% using the hammer to 90% the pill crusher) stated that if OC tablets were available to them, they would use the methods provided in order to tamper with the tablets. By contrast, none of the subjects (15 total) who attempted to use a pill crusher on OTR tablets, felt this mode of tampering was feasible. Less than 50% of the subjects

Reference ID: 3192781

(range 25% for the mortar and pestle to 45.5% for X-Acto knife), felt the methods they were using could be used to tamper with the OTR tablets.

For both OC tablets (70% to 94%) and OTR (93% to 100%), subjects reported that they would also use a different method of tampering than the one they were using.

Reference ID: 3192781

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

/s/

JAMES M TOLLIVER
09/21/2012

SILVIA N CALDERON
09/21/2012

MICHAEL KLEIN
09/21/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 21, 2012

To: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: IND 29,038 Sequence 0025 (693) - Oxycodone HCl with cross reference to NDA 22, 272 for OxyContin Controlled-Release Tablets approved April 5, 2010
Indication: Relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Dosages: 30 Oxycodone HCl Tablets
Sponsor: Purdue Pharma L.P.

Materials reviewed: Clinical Study Report OTR1018 entitled "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. (Module 5.3.1.2)

I. Background

In a letter dated September 16, 2010, Purdue Pharma L.P. submitted under IND 29,038 a final study report for clinical study OTR1018 entitled "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." The application was cross referenced to NDA 22,272 for OxyContin Controlled-Release Tablets approved on April 5, 2010.

Subsequently, the Sponsor submitted Citizen Petition FDA 2012-P-0760 dated July 13, 2012, requesting that FDA require that generics referencing reformulated OxyContin (oxycodone hydrochloride extended release) be shown to perform as well as OxyContin when subjected to known and anticipated forms of tampering for purposes of abuse and misuse. As part of the basis for this petition, the Sponsor documented the result obtained from clinical study OTR1018.

Reference ID: 3192768

In response to the citizen's petition, CSS has reviewed clinical study OTR1018. The review and conclusions reached by CSS are provided below.

II. Conclusions:

Based on the review of clinical study OTR1018, CSS has the conclusions listed below.

- Overall, study OTR1018 provides some evidence that 30 mg Oxycodone HCl Tamper Resistant Tablets (OTR) may be less susceptible to intranasal abuse than the original formulation of 30 mg OxyContin and 30 mg Oxycodone HCl API. However, 30 mg OTR is not without abuse potential by the intranasal route of administration.

- The intranasal administration of finely crushed and coarsely crushed 30 mg OTR, as well as crushed 30 mg original OxyContin and powdered 30 mg Oxycodone API, resulted in levels of "drug liking" and "high" that were significantly greater than that produced by intranasal administration of placebo. Intranasal administration of finely crushed 30 mg OTR, crushed 30 mg OxyContin (OC), and powdered 30 mg Oxycodone HCl API, <u>but not coarsely crushed 30 mg OTR</u>, produced significantly greater levels of "Overall Drug Liking" compared to placebo.

- Group statistics and individual responder analysis reveals that the intranasal administration of finely crushed or coarsely crushed 30 mg OTR is generally associated with a statistically, significantly lower level of drug liking compared to similar administration of finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API. This is evidenced by the following:

    - The median "drug liking" VAS scores following intranasal finely crushed 30 mg OTR (87) and coarsely crushed 30 mg OTR (68) were significantly lower than the median scores following either finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API (both 100)

    - Overall, approximately 37.0% (10 out of 27 total subjects) and 33.3% (9 out of 27 total subjects) had at least 30% reduction in Emax of "drug liking" following intranasal treatment with finely crushed 30 mg OTR as compared to intranasal administration with either finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API.

    - Overall approximately 55.6% (15 out of 27 total subjects) and 48.1% (13 out of 27 total subjects) had at least 30% reduction in Emax of "drug liking" following intranasal administration of coarsely crushed 30 mg OTR compared to either finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API.

- Individual responder analysis identified subgroups of the subject population (N=27) who upon intranasal administration of finely crushed 30 mg OTR (9 and 8 out of 27 subjects, respectively) or coarsely crushed OTR (6 and 6 out of 27 subjects, respectively) experienced

Reference ID: 3192768

a level of "drug liking" that was not significantly different from the level of "drug liking" they experienced following intranasal administration of 30 mg finely crushed OxyContin or powdered 30 mg Oxycodone HCl API. These same individuals responded with "drug liking" VAS scores of greater than 95 following intranasal administration of either finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API.

- As determined using the unipolar "High" VAS, intranasally administered 30 mg OTR (finely and coarsely crushed) produced significantly greater levels of "high" (LS means of 72.88 and 59.25, respectively) compared to placebo (LS mean of 24.36) but significantly lower levels of "high" as produced by intranasal administration of either finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API (LS means of 91.87 and 86.54, respectively).

- As determined using the bipolar "Overall Drug Liking" VAS, intranasal administration of finely crushed OTR (median Emax of 73), but not coarsely crushed OTR (median Emax of 51), produced an overall drug liking significantly greater than that of placebo (median Emax of 51). The overall drug liking produced by finely crushed 30 mg OTR was significantly lower than either finely crushed 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API (median Emax of 100 and 95, respectively.

- Overall, the results provided by the Sponsor regarding pharmacokinetic analysis of oxycodone demonstrated that intranasal administration of finely crushed OTR or coarsely crushed OTR resulted in lower oxycodone maximum plasma concentrations (Cmax), greater time to achieve oxycodone Cmax (Tmax) compared to the intranasal application of either finely crushed OxyContin or powdered 30 mg Oxycodone HCl API. Total oxycodone exposure was similar across treatments. The reduction in oxycodone Cmax and increase in oxycodone Tmax, along with no change in total drug exposure, is supportive of a reduced susceptibility to intranasal abuse of 30 mg OTR compared to intranasal abuse of 30 mg original OxyContin or powdered 30 mg Oxycodone HCl API.

    - An unexpected finding of the pharmacokinetic analysis was that treatment with 30 mg finely crushed OTR and coarsely crushed 30 mg OTR resulted in similar oxycodone Cmax values [mean (SD) = 29.4 (7.71) and 29.8 (12.2) ng/mL], respectively. The implication is that the finely crushed OTR consists of a lower particle size distribution than does coarsely crushed OTRc. Results of *in vitro* physical manipulation and chemical extraction studies on the reformulated OxyContin, showed a greater release of oxycodone with a decrease in particle size (DAARTS, CSS Review NDA 22272, September 4, 2009, Author James Tolliver, Ph.D.,). Unfortunately, the Sponsor did not provide any details characterizing the appearance and particle size distribution of the various treatments. In addition, no information was provided regarding the procedures for preparing the various crushed treatments. Such information should have been provided and should be required for studies of this type.

- Results suggest that nasal irritation most likely will not be a deterrent to the intranasal abuse of 30 mg OTR tablets, at least as administered in this study. Both observer-rated (Ear, Nose

Reference ID: 3192768

and Throat Specialist) and subject-rated assessments revealed that categories of clinical findings and complaints, utilized as reflecting evidence of nasal irritation, were detected in a subset of the total treatment population. These clinical findings and subject reported complaints were in the majority of cases documented in severity as "Very Mild Problem" to “Mild/Slight."

III. Review of Clinical Study OTR1018

Study OTR1018 was a single-center, double-blind study in non-dependent, recreational opioid users to evaluate the abuse potential, pharmacokinetics, and safety of intranasally administered crushed oxycodone HCl tamper resistant (OTR) tablets. This study was sponsored by Purdue Pharma, L.P. and conducted by an independent contract research organization, (b) (4) (b) (4). Study was conducted under a controlled clinical setting.

The objectives of study OTR1018 included the following:

- To evaluate intranasal abuse potential and pharmacodynamic effects of coarsely and finely crushed OTR compared to finely crushed original OxyContin (OC), powdered oxycodone active pharmaceutical ingredient (API) (Oxy API), and an OxyContin 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 recreational opioid users with a history of intranasal abuse, and
- To determine the comparative pharmacokinetics of intranasally administered crushed OTR compared to crushed OC and Oxy API.

A total of 30 subjects successfully completed the screening and qualification phase and cleared for participation in the treatment phase. These subjects successfully satisfied among others the following criteria:

- Displayed a lack of opioid dependence as evidenced in a naloxone (0.2 mg i.v. bolus) challenge test (assessment using the Objective Opiate Withdrawal Scale (COWS)).
- Display a peak score for lactose powder placebo $\leq$ 55 on the bipolar Drug Liking Visual Analogue Scale (VAS) and $\leq$ 10 on the High VAS. **OR** Display a peak score for 30 mg Oxy API greater than placebo by at least 15 points on the bipolar Drug Liking VAS and by at least 30 points on the unipolar High VAS.
- Achieved acceptable responses to lactose powder placebo and Oxy API 30 mg on Drug Liking VAS, Good Effects VAS, Bad Effects VAS, High VAS, and Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG), as judged by the investigator and/or designee.
- Ability to tolerate 30 mg Oxy API, as judged by the investigator or designee.
- Displayed general behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

In the Treatment Phase, treatments were administered in randomized order, according to treatment sequences created from two 5 x 5 Williams squares. There were five Treatment Phase

Reference ID: 3192768

visits with each visit lasting 3 days during which subjects remained at the study site. The washout period between the Treatment visits was generally 7 days and no less than 2 days. The following five treatments (one treatment per visit) were administered:

- 30 mg coarsely crushed OTR tablets (OTRc)
- 30 mg finely crushed OTR tablets (OTRf)
- 30 mg finely crushed OC tablets (OC)
- 30 mg Oxy API powder (OxyAPI)
- finely crushed OC placebo (PL)

Information in the study report was not provided regarding the specific methods used to prepare the crushed treatments. In addition, no information was provided regarding physical characteristics, including particle size distribution for each of the treatments.

At the time of each treatment, subjects were required, using a straw, to insufflate the study drug as quickly as possible, with an allocated maximum dose window of 5 minutes. At each dosing, drug was administered to one nostril, with the other nostril serving as a control. Subjects could switch nostrils between treatment visits.

A number of pharmacodynamic measurements were determined in this study. However, for purposes of this review, the only pharmacodynamic measurements evaluated will include:

- Bipolar Drug Liking Visual Analog Scale (VAS)
- Unipolar High VAS
- Bipolar Overall Drug Liking VAS

The principle parameter assessed with each of the pharmacodynamic measurements was Emax. The Drug Liking VAS and High VAS were administered at 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dosing. The High VAS will also be given just prior to dosing (pre-dose). The Overall Drug Liking VAS was administered only at 8 hours and 24 hours post-dose. The Drug Liking VAS and High VAS reflect "at the moment" subjective effects. In contrast, when answering the Overall Drug Liking VAS, subjects were instructed to base their responses on the cumulative or overall assessment of the drugs effects.

Blood sampling for pharmacokinetic assessment for oxycodone was taken pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dosing. Pharmacokinetic endpoints determined included:

- Cmax: maximum oxycodone plasma concentration
- Tmax: time to reach maximum oxycodone plasma concentration
- AUClast: area under the oxycodone concentration time curve from time zero to last assessment
- AUCinf: area under the oxycodone concentration time curve from time zero to infinity
- plasma concentrations over time for oxycodone.

Study included evaluations of nasal irritation from intranasal administration of each treatment. Assessments of irritation were completed by an Ears, Nose, and Throat (ENT) specialist, using

Reference ID: 3192768

endoscopy and intranasal photography and by each study subject. Assessment by the ENT specialist, conducted approximately 30 minutes post-dosing focused on the categories of nasal congestion, nasal irritation (external) and nasal discharge. The subject rated assessment, conducted at selected times post-dosing focused on the categories of burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion. For all categories, observations were rated on a 6-point scale consisting of: 0 = Not observed/No problem, 1 = Very Mild Problem; 2 = Mild / Slight Problem; 3 = Moderate Problem; 4= Severe Problem; and 5 = Very Severe Problem / "As Bad as Can Be."

Results

Subjective Effects

Although the Sponsor evaluated the effects of treatment on a variety of subjective measures, this review focuses on the effects of treatment on three subjective measures including Drug Liking VAS, Overall Drug Liking VAS and High VAS. Statistical analysis for the measures was conducted by the Office of Translational Science, Office of Biostatistics within FDA/CDER (DAARTS, August 20, 2012, Author: Ling Chen, Ph.D.). Analysis was based on a 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. The primary endpoint was the maximum pharmacodynamic effect (Emax) for each subjective measure. If predose response was collected, Emax was calculated based on change from predose responses.

All four active drug treatments produced drug liking. Mean (Standard Error) scores for Emax on the bipolar Drug Liking VAS for OCf, OTRc, OTRf, and Oxy API were 93.78 (2.76), 71.70 (4.28), 79.33 (4.08) and 88.56 (3.27), respectively. Median Emax scores were 100, 68, 87, and 100 for OCF, OTRC, OTRF, and Oxy API, respectively.

Statistical analysis of treatment comparisons using median values of Emax for Drug Liking revealed the following:

- Median Emax values of drug liking produced by each of the active treatments were significantly higher than the median Emax produced by placebo.
- Median Emax values of drug liking from treatments with OTRf and OTRc were significantly lower than those following treatments with either OCf or Oxy API.
- Although the median Emax value for drug liking was numerically higher following treatment with OTRf compared to OTRc, the difference between these treatments was not statistically significant.
- Although treatments with OCf and Oxy API resulted in median Emax values for drug liking of 100, analysis by the Wilcoxon sign-rank test showed that the median of OCf was actually significantly greater than that from treatment with Oxy API.

Reference ID: 3192768

An analysis of Emax values of drug liking for each individual revealed substantial variability between subjects of Emax values achieved. Some significant observations from this analysis were the following:

- The percentages of subjects who had Emax of Drug Liking VAS for OCf and Oxy API greater than 95 were approximately 77.8% (21/27) and 59.3% (16/27), respectively.
- For those subjects displaying an Emax of Drug Liking VAS greater than 95% for the positive control drugs
    - 56.3% (9/16) and 38.1% (8/21) of subjects had no reduction for OTRf relative to OCf and Oxy API, respectively
    - 28.6% (6/21) and 37.5% (6/16) of subjects had no reduction for OTRC relative to OCf 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 drug liking for OTRf 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 of Emax of drug liking for OTRc relative to OCf and Oxy API.

The mean (Standard Error) of the Emax from the Overall Drug Liking VAS for the treatments OCf, OTRc, OTRf, Oxy API, and placebo were 86.96 (4.34), 59.63 (4.48), 67.78 (5.70, 83.93 (3.73), and 50.63 (2.32), respectively. Corresponding median values of Emax overall drug liking were 100, 51, 73, 95, and 51, respectively.

Statistical analysis of treatment comparisons for overall median values of Emax overall drug liking showed that treatments with OCf, Oxy API, or OTRf, <u>but not with OTRc</u>, resulted in significantly greater levels of overall drug liking compared to placebo treatment. Treatment with OTRF was associated with a 27% and 23% reduction in medium Emax overall liking score compared to treatment with OCf and Oxy API, respectively. The median Emax overall liking score for OTRf treatment was just statistically ($p < 0.426$) higher than the Emax overall liking score for OTRc treatment.

The LS mean scores for Emax on the unipolar "High" VAS following treatment with OCf, OTRf, OTRc, Oxy API, and placebo were 91.87, 72.85, 59.25, 86.54, and 24.36, respectively. Statistical analysis of differences in LS means between treatments demonstrated the following:

- All four active treatments produced statistically greater levels of high VAS compared to treatment with placebo.
- On the High VAS, treatment with OCf and Oxy API produced significantly higher means compared to treatment with OTRf and OTRc.
- Treatment with OTRf produced a statistically higher LS mean on the High VAS than did treatment with OTRc.

Pharmacokinetics of Oxycodone

The Sponsor provided descriptive statistics (mean(SD), median, range, and geometric mean) for the pharmacokinetic parameters measured including Cmax, Tmax, AUClast, and AUCinf.

Reference ID: 3192768

Overall, the results demonstrated that intranasal administration of OTRf or OTRc resulted in lower oxycodone Cmax, higher oxycodone Tmax compared to the intranasal application of the positive comparators, OCf and Oxy API. Total oxycodone exposure was similar across treatments.

Intranasal administration of OTRc and OTRf resulted in similar mean Cmax values [Mean (SD) of 29.4 (7.71) and 29.8 (12.2) ng/mL, respectively]. Intranasal administration of OC and Oxy API produced Cmax mean values that were approximately 2 [mean (SD) of 59.6 (16.2)] and 1.8 times higher [52.1 (13.0) ng/mL)], respectively.

The time to reach Cmax, i.e. Tmax, was shorter following intranasal administration of the positive comparators, OC and OxyAPI (median of 1.10 and 1.00 hrs, respectively) compared to similar administration of either OTRf (2.08 hrs) or OTRc (2.62 hrs). A particularly wide range of Tmax values was achieved following intranasal administration of OTRc (0.25 to 8.1 hrs) and OTRf (1.07 to 6.07 hrs).

According to the Sponsor, values for AUClast and AUCinf were similar across all treatments with only a slightly lower trend for OTRf and OTRc compared to OCf and OxyAPI. This indicated that, in general, total exposure to oxycodone was similar across treatments. However, compared to the other treatments, intranasal administration of coarsely crushed OTR resulted in a wide range for AUClast (41.2 to 726 ng/mL*hr) and AUCinf (42 to 819 ng/mL*Hr). This indicated greater variability in total oxycodone exposure following intranasal administration of coarsely ground OTR tablets.

Evaluation of Nasal Irritation

Both observer-rated and subject-rated evaluations of nasal irritation collectively suggest that the specific intranasal treatments administered in this study, including OTRf and OTRc, produced at most limited intranasal irritation. The different categories of complaints reflecting intranasal administration were expressed in a limited subgroup of the total treatment population. The vast majority of the complaints were rated in the range of "Very Mild Problem - Mild/Slight Problem." It is certainly questionable as to what extent, if any nasal irritation would have a deterrent effect to administration of OTR tablets as used in this study. One observation of this assessment was that observer-rated evaluations revealed a much lower incidence of nasal irritation than did the subject-rated evaluation. This may have resulted in part from 1) the single assessment at about 30 minutes conducted by the ENT specialists as opposed to the multiple time course assessments by the subject; and 2) the possible negative ENT specialist finding is subjects reported only "Very Mild Problem - Mild/Slight Problem" complaints.

Twenty-nine subjects were assessed by an ENT specialist for nasal congestion, nasal irritation and nasal discharge approximately 30 minutes following intranasal administration of study drugs and placebo. Of individuals receiving OTRf treatment, 7 and 3 were determined to have "very mild" and "mild" nasal congestion, respectively. "Very mild" nasal congestion was also found in 3 subjects receiving OTRc, 3 subjects receiving OCf and 1 subject receiving OxyAPI.

Reference ID: 3192768

The category of "nasal irritation" was documented as "very mild" in two subjects, one receiving OTRf and the other receiving Oxy API. The third category, namely "nasal discharge," was documented as "very mild" in two subjects, one receiving OTRf and the other receiving OTRc.

Subject rated evaluation of nasal irritation showed that all five intranasal treatments, including placebo, given in this study produced some nasal irritation in a subgroup of the total treatment population of 29 subjects. The treatment least frequently associated with complaints reflecting nasal irritation was Oxy API. Across all six categories of assessment of nasal irritation, the vast majority of subjects who expressed a complaint reflecting nasal irritation assessed the severity in the range of "Very Mild Problem - Mild/Slight Problem."

The "Need to Blow Nose" was the most frequently mentioned complaint reflecting "nasal irritation." Of 29 total subjects administering intranasal OTRf, 18 subjects reported a feeling of needing to blow the nose. Of those 18 subjects, the need to blow the nose was rated as "Very Mild Problem" by 10 subjects, as Mild/Slight Problem" by 4 subjects, as "Moderate Problem" by 3 subjects, and as a "Severe" problem by 1 subject. Among the same 29 total subjects, following treatment with intranasal OTFc, 13 subjects reported feeling the need to blow the nose with a severity of "Very Mild Problem" by 6 subjects, "Mild/Slight Problem" by 4 subjects, and "Moderate Problem" by 3 subjects. Following intranasal treatment with Placebo, OCf, and Oxy API, the number of subjects (out of 29 total) complaining of need to blow nose were 8, 14, and 6, respectively. Of these 28 total (8 + 14 + 6) complaints, 20 were reported in the severity range of "Very Mild Problem to Mild/Slight Problem."

The category of 'Nasal Congestion" was the second most frequent complaint reflecting nasal irritation. Of 29 total subjects receiving intranasal placebo, OTRf, OTRc, OCf, and Oxy API, the number of subjects expressing nasal congestion after each treatment were 7, 15, 14, 8, and 6, respectively. Of the 29 (15 +14) complaints of nasal congestion from subjects following administration of either OTRf or OTRc, 20 complaints were rated in the range of "Very Mild Problem" to Mild/Slight Problem." Only one complaint each of nasal congestion following OTRf treatment was rated as "Severe Problem" and "Very Severe Problem / "As Bad as Can Be."

Complaints of "Burning", "Nasal Discharge", and "Facial Pain/Pressure" were less frequently reported. However, some complaints under each of these categories were reported following intranasal administration of each of the treatments, including placebo. The vast majority of these complaints were rated in severity in the range of "Very Mild Problem" to Mild/Slight Problem."

Reference ID: 3192768

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

/s/

JAMES M TOLLIVER
09/21/2012

SILVIA N CALDERON
09/21/2012

MICHAEL KLEIN
09/21/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 21, 2012

To: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: IND 29,038 Sequence 0025 (693) - Oxycodone HCl with cross reference to NDA 22, 272 for OxyContin Controlled-Release Tablets approved April 5, 2010
Indication: Relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Dosages: 30 Oxycodone HCl Tablets
Sponsor: Purdue Pharma L.P.

Materials reviewed: Clinical Study Report OTR1016 entitled "A Randomized, Open-Label, Single-Dose, Crossover Study of the Effects of Various Tampering Methods on Exposure to Oxycodone in Fasting Healthy Subjects." (Module 5.3.1.1)

I. Background

In a letter dated September 16, 2010, Purdue Pharma L.P. submitted under IND 29,038 a final study report for clinical study OTR1016 entitled "A Randomized, Open-Label, Single-Dose, Crossover Study of the Effects of Various Tampering Methods on Exposure to Oxycodone in Fasting Healthy Subjects." The application was cross referenced to NDA 22,272 for OxyContin Controlled-Release Tablets approved on April 5, 2010.

Subsequently, the Sponsor submitted Citizen Petition FDA 2012-P-0760 dated July 13, 2012, requesting that FDA require that generics referencing reformulated OxyContin (oxycodone hydrochloride extended release) be shown to perform as well as OxyContin when subjected to known and anticipated forms of tampering for purposes of abuse and misuse. As part of the basis for this petition, the Sponsor documented results from clinical study OTR1016.

In response to the citizen's petition, CSS has reviewed clinical study OTR1016. The review and conclusions reached by CSS concerning the study are provided below.

Reference ID: 3192731

II. Conclusions:

CSS reaches the following conclusions based upon a review of study OTR1016;

- Rigorous chewing of intact, crushed, or pre-softened OTR 40 mg tablets substantially compromises the controlled release mechanism for oxycodone. This is evident by an increase in oxycodone Cmax. The Cmax was equivalent to the Cmax achieved following ingestion of chewed OxyContin 40 mg tablet or IR 40 mg oxycodone solution, and by a reduction in the time to reach Cmax (Tmax).

- The OTR formulation was less susceptible to compromise of oxycodone release than was the OxyContin formulation following "normal" chewing as evidenced by a 23.6% lower least square (LS) mean oxycodone Cmax value and an approximately 2-fold longer Tmax.

- "Crushing" of an OTR tablet using a mortar and pestle, followed by ingestion, did not compromise the controlled release properties for oxycodone.

- Ingestion of an intact OTR 40 mg tablet resulted in total oxycodone exposure similar to that following ingestion of either intact OxyContin 40 mg tablet or immediate release (IR) 40 mg oxycodone HCl in solution. Manipulation of the OTR 40 mg tablet by crushing with mortar and pestle, chewing or pre-softening, did not affect the total exposure to oxycodone.

- Looking at the results of this study in light of the relationship of oxycodone plasma levels and drug liking effects as revealed on human abuse potential study OTR1018 sponsored by Purdue Pharma it is predicted that vigorous chewing followed by ingestion of either an OTR 40 mg tablet, a crushed (mortar and pestle) OTR 40 mg tablet or a pre-softened OTR 40 mg tablet will produce significant levels of drug liking on the Drug Liking Visual Analog Scale, thereby provided evidence of substantial subjective reinforcing effects.

III. Review of Clinical Study OTR1016

Clinical study OTR1016 was designed to examine the effects of selected modes (chewing and crushing) of physical manipulation on the release of oxycodone from OTR and OC tablets. The study was conducted in healthy subjects under naltrexone blockade to minimize opioid-related adverse events. The study is divided into Parts A, B, and C.

Part A is a randomized, open-label, single-dose, 8-treatment, 5-period, incomplete block, crossover study using fasting adult male and female subjects. At total of 62 subjects were randomized to treatment with 48 completing the study and 14 discontinuing the study. Subjects were required to vigorously chew OTR and OC tablets for up to 10 minutes followed by swallowing of remaining contents. Treatments include the following:

- OTR 40 mg tablet swallowed intact
- OTR 40 mg tablet chewed and swallowed

Reference ID: 3192731

- OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, and swallowed
- OTR 40 mg tablet particle size reduced by crushing via mortar and pestle, chewed, and swallowed.
- OTR 40 mg tablet pre-softened in water, chewed, and swallowed
- OxyContin 40 mg tablet swallowed intact
- OxyContin 40 mg tablet chewed and swallowed
- Immediate-release 40 mg oxycodone solution

Other than noting the use of a mortar and pestle, the study report did not provide any other detailed information regarding the procedure for crushing OTR 40 mg and OC 40 mg tablets. In addition, no information was provided regarding the particle size distribution of the powdered material.

Parts B and C are randomized, open-label, single-dose, 4-period, 2-treatment, replicated designs intended to look specifically at the effects of "vigorous chewing" (Part B) and "normal chewing" on release of oxycodone HCl from OTR and OC tablets. Part C characterizes release of oxycodone from the formulation following chewing in a manner that would be considered accidental or inadvertent. For Parts B and C, 26 subjects were randomized to treatment with 21 and 23 subjects, respectively, completing the study. The specific treatment arms for Parts B and C include:

- OTR 40 mg tablet chewed and swallowed
- OxyContin 40 mg tablet chewed and swallowed.

For all three parts (A, B, and C) of the overall study, subjects were required to satisfactorily complete a qualification phase prior to entering the treatment phase. Subjects intended for parts A and B were required to vigorously chew (for no more than (b) (4) each) alternating single OC placebo and OTR placebo tablets, with optional 5 minute rest periods between tablet administrations. Subjects who did not tolerate this session were excluded from the study. For Part C, subjects chewed normally 3 OC placebo tablets, with optional 5 minute rest periods. The median of the 3 chewing durations was used to establish the maximum chewing duration during the randomized portion of Part C on an individual bases.

Blood samples for determining oxycodone concentrations were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36m 48 and 72 hours post-dosing. Specific pharmacokinetic variables of interest for oxycodone were determined for each subject following treatment: maximum observed plasma concentration (Cmax); time to reach maximum plasma concentration (Tmax); area under the plasma concentration-time curve from 0 h to the last measurable plasma concentration (AUCt); and the area under the plasma concentration-time curve extrapolated to infinity (AUCfin). Both AUCt and AUCfin were used to determine total drug exposure for a given treatment. In secondary analysis, the following parameters (ratios) were determined: Cmax (test treatment)/Cmax (reference treatment) (RCmax); AUCt(test treatment)/AUCt(reference treatment) (RAUCt); and AUCinf(test treatment)/AUCinf(reference treatment).

Reference ID: 3192731

Results

Part A.

Statistical analysis conducted by the Sponsor using LS means and confidence intervals demonstrated that values of oxycodone AUCt and AUCinf were equivalent for all eight treatments given under Part A. LS means for oxycodone AUCt were in the range of 414 to 455 ng*h/mL while LS means for oxycodone AUCinf ranged from 415 to 459 ng*h/mL. The data indicate that the 8 treatments resulted in similar total exposures to oxycodone.

Statistical analysis reported by the Sponsor using LS means and confidence intervals of oxycodone Cmax values among the different treatments revealed the following results:

- Vigorous chewing followed by ingestion of either an OTR 40 mg tablet, a crushed (mortar and pestle) OTR 40 mg tablet or a pre-softened OTR 40 tablet results in oxycodone Cmax values (LS means of 70.5, 69.7, and 72.9 ng/mL, respectively). These values are greater than the oxycodone Cmax (LS mean of 41.1 ng/mL) following ingestion of an intact OTR 40 mg tablet, but equivalent to the oxycodone Cmax values achieved with ingestion of either rigorously chewed OxyContin 40 mg tablet (LS mean of 80.6 ng/mL) or ingestion of IR 40 mg Oxycodone oral solution (LS mean of 76.2 ng/mL).
- Ingestion of an OTR 40 mg tablet initially crushed using a mortar and pestle as carried out in this study resulted in an oxycodone Cmax (LS mean of 42.7 ng/mL) that was equivalent to the Cmax (LS mean of 41.1) following ingestion of an intact OTR 40 mg tablet.
- Equivalent oxycodone Cmax values are obtained following ingestion of an intact OTR 40 mg tablet (LS mean of 41.1 ng/mL) and ingestion of an intact OxyContin 40 mg tablet (LS mean of 39.3 ng/mL).

Examination of median (min, max) values of Tmax among the treatments showed that chewing followed by swallowing either the intact OTR tablet [1.5 (0.5,5) hrs], crushed OTR tablet [1.5 (0.75, 3.5) hrs] or pre-softened OTR tablet [1.5 (0.75, 4.5) hrs] reduced the Tmax for oxycodone compared to the Tmax for swallowing the intact OTR tablet [4.5 (3.0, 8.0) hrs]. These reduced Tmax values were only a little longer than the Tmax values of oxycodone resulting from either chewing and swallowing an OxyContin tablet [1.0 (0.75, 3.00) hrs] or ingesting an IR 40 mg oxycodone solution [1.00 (0.50, 4.00) hrs. An additional observation from this study was that the ingestion, without chewing, of an OTR tablet initially crushed using a mortar and pestle, produced at most a modest decrease in Tmax for oxycodone when compared to ingestion of an intact OTR tablet (median of 3.75 hrs compared to 4.50 hours, respectively).

Part B.

Statistical analysis completed by the Sponsor demonstrated that vigorous chewing of an OTR 40 mg tablet and an OxyContin 40 mg tablet resulted in closer similar values of Cmax (LS means of 68.3 versus 79.0 ng/mL, respectively), AUCt (LS means of 388 versus 412 ng*h/mL, respectively) and AUCinf (LS means of 389 and 415 ng*h/mL, respectively). Median (min, max) values of Tmax for chewed OTR 40 mg tablet and OxyContin 40 mg tablet were 1.50 (0.62, 3.75) hrs and 1.00 (0.50, 4.50) hrs, respectively.

Reference ID: 3192731

Part C.

According to the Sponsor, statistical analysis revealed that normal, non-vigorous, chewing, followed by swallowing, of OTR 40 mg tablet and OxyContin 40 mg tablet produced similar total drug exposure as evident by AUCt (LS Means of 398 verses 414 ng*h/mL, respectively) and AUCinf (LS Means of 402 and 415 ng*h/mL, respectively). However, oxycodone LS mean Cmax was 23.6% lower (54.9 ng/mL versus 71.9 ng/mL) following normal chewing of OTR 40 mg tablet compared to normal chewing of OxyContin 40 mg tablet. This difference was determined to be significant as 90% confident intervals were not entirely contained in the 80 to 125% interval.

The time to reach Cmax (Tmax) was approximately twice as long following normal chewing of the OTR 40 mg tablet [median (min,max) = 2.38 hours (1.00, 4.75 hr)] compared to Tmax following normal chewing of OxyContin 40 mg tablet [median (min,max) = 1.13 hours (0.625, 2.50 hr)]

Predicted Subjective Reinforcing Effects

Subjective reinforcing effects were not measured in this study. However, it is possible to predict the possible subjective reinforcing effects of the treatments in this study by examining the pharmacokinetic results in light of pharmacokinetic parameters for oxycodone and subjective reinforcing effects observed in human abuse potential study OTR1018 sponsored by Purdue Pharma.

Study OTR1018 looked at the pharmacokinetics of oxycodone and the subjective reinforcing effects produced following intranasal administration of placebo, crushed 30 mg OTR tablets, finely crushed original 30 mg OxyContin and powdered 30 mg Oxycodone HCl API. Of particular interest for this review was the finding following treatment with crushed 30 mg original OxyContin and powdered 30 mg Oxycodone HCl API. These two treatments resulted in a mean (SD) oxycodone Cmax of 59.6 (16.2) ng/mL and 52.1 (13.0) ng/mL, respectively. Both Cmax values were achieved within approximately 1 hour (Tmax) post-dose. In addition, using the bipolar Drug Liking Visual Analog Scale (VAS), intranasal treatment with 30 mg crushed OxyContin and 30 mg Oxycodone HCl API was found to produce high reinforcing effects as evidenced by high scores on the Drug Liking VAS [mean (SE) of 93.78 (2.76) and 88.56 (3.27), respectively].

In the current study, vigorous chewing followed by ingestion of either an OTR 40 mg tablet, a crushed (mortar and pestle) OTR 40 mg tablet or a pre-softened OTR 40 mg tablet results in oxycodone Cmax values [means (SD) of 74.1 (19.1), 72.6 (22.2, and 77.2 (19.4) ng/mL, respectively]. These Cmax values for the most part (statistical comparisons not made) were higher than the Cmax values achieved in study OTR1018 and were accompanied by high levels of drug liking on the Drug Liking VAS. In addition, the Tmax values following the three treatments (each 1.5 hours) are close to the Tmax values (about 1 hour) found in study OTR1018.

Reference ID: 3192731

Assuming that across studies there is a similar correlation of oxycodone plasma concentrations to drug liking scores on the Drug Liking VAS, it is predicted that vigorous chewing followed by ingestion of either an OTR 40 mg tablet, a crushed (mortar and pestle) OTR 40 mg tablet or a pre-softened OTR 40 mg tablet will produce significant levels of drug liking indicative of positive subjective reinforcing effects.

Reference ID: 3192731

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

/s/

JAMES M TOLLIVER
09/21/2012

SILVIA N CALDERON
09/21/2012

MICHAEL KLEIN
09/21/2012

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 21, 2012

To: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: IND 29,038 Sequence 0025 (693) - Oxycodone HCl with cross reference to NDA 22, 272 for OxyContin Controlled-Release Tablets approved April 5, 2010
Indication: Relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.
Dosages: 30 Oxycodone HCl Tablets
Sponsor: Purdue Pharma L.P.

Materials reviewed: Clinical Study Report OTR1022 entitled "Single-Center, Randomized, Cross-Over Study in Recreational Opioid Users to Evaluate the Safety of Crushed and Intranasally Administered OTR and OC Placebo Tablets" (Module 5.3.1.2)

I. Background

In a letter dated September 16, 2010 Purdue Pharma L.P. submitted under IND 29,038 a final study report for clinical study OTR1022 entitled "Single-Center, Randomized, Cross-Over Study in Recreational Opioid Users to Evaluate the Safety of Crushed and Intranasally Administered OTR and OC Placebo Tablets." The application was cross referenced to NDA 22,272 for OxyContin Controlled-Release Tablets approved on April 5, 2010. CSS has reviewed clinical study OTR1022. The review and conclusions reached by CSS are provided below.

II. Conclusions:

- Observer-rated (endoscopic evaluation) and subject-rated assessment of nasal irritation indicates that the intranasal administration of fine powder and coarse powder from 20 mg oxycodone tamper-resistant (OTR) placebo tablets and of fine powder from placebo tablets of originally formulated 20 mg OxyContin produces at most limited nasal irritation.

Reference ID: 3192931

- The only statistically significant finding was a greater subject reporting of "nasal congestion" following intranasal administration of OTR placebo fine powder compared to intranasal administration of original OxyContin placebo find powder. The low "nasal congestion" score (mean (SD) = 1.1 (1.45) indicates that the nasal congestion following OTR placebo fine powder treatment was in the range of "Very Mild Problem" to Moderate Problem."

- The effects of the non-active components of the formulations for oxycodone tamper-resistant tablets and for the originally formulated OxyContin tablets on nasal irritation would not be expected, at least under the conditions of this study, to be a deterrent to the intranasal abuse of these two products.

III. Review of Clinical Study OTR1022

Clinical study OTR1022, completed in July 2009, was sponsored by Purdue Pharma L.P. and conducted by an independent contract research organization, (b) (4). The study was conducted at a single site in (b) (4) namely the (b) (4). All subjects (N = 10) were recruited and enrolled from this site.

Objectives of the study included the evaluation of the safety and tolerability of intranasally administered coarsely and finely crushed oxycodone tamper-resistant (OTR) placebo tablets (OTR-PBO) compared to originally formulated OxyContin (OC) placebo tablets (OC-PBO) in healthy, adult, non-dependent, recreational opioid users with a history of intranasal abuse.

Twenty-three subjects were screened, while 11 subjects were actually enrolled. One subject was lost to follow-up after treatment visit 2. Ten subjects completed the study and were included in the subjective tolerability analysis.

Placebos for OC 20 mg tables and for OTR 20 mg tablets were supplied by Purdue Pharma. OC-PBO tablets differed from active OC tablets only in having the oxycodone replaced with lactose. The only difference between OTR-PBO tablets and active OTR tablets was that OTR-PBO tablets contained microcrystalline cellulose in place of oxycodone HCl.

The treatment phase consisted of 3 visits, occurring over 3 consecutive days, during which subjects received the following treatments (different one each day):

- OTR-PBO (20 mg) finely crushed OTR placebo tablet
- OTR-PBO (20 mg) coarsely crushed OTR placebo tablet
- OC-PBO (20 mg) finely crushed originally formulated OxyContin placebo tablet

Treatments were randomized with treatment sequence following two 3 x 3 Williams Squares design. The washout period between treatments is at least 24 hours. Due to the difference in granularity (fine versus coarse) of the placebo treatments, the study was only partially blind. Subjects self-administered all placebos under the supervision of the study site investigator or designated study personnel.

Reference ID: 3192931

Subjects were required to insufflate the powdered material in one nostril within 5 minutes using a straw. The other nostril served as a control nostril. The crushing methods were selected based upon the results of a previously conducted in vitro study, but were not provided in current study report.

Observer- and subject-rated assessments of nasal irritation were conducted to evaluate subjective tolerability of the treatments. Observer rated assessment was based on the following three categories: 1) nasal congestion; 2) nasal irritation; and 3) nasal discharge. Subject rated assessment used the following five categories: 1) burning, 2) Need to Blow Nose; 3) Runny Nose/Nasal Discharge; 4) Facial pain/pressure; and 5) nasal congestion. For observer rated assessment an Ear, Nose, and Throat (ENT) specialist (based on endoscopic examination) rated each of these categories on a 6 point scale: 0 = Not observed/No problem, 1 = Very Mild Problem; 2 = Mild/Slight Problem; 3 = Moderate Problem; 4 = Severe Problem; to 5 = Very Severe Problem/"As Bad as Can Be." The same 6-point scale was used for the subject rated assessment. Information was not provided regarding the validation of this scale.

Results

Observer-Rated Assessment of Intranasal Irritation

Endoscopic examination of the ten subjects reviewed: 1) very mild nasal irritation in 3 subjects following treatment with OTR-PBO fine powder; 2) nasal irritation in 1 subject following treatment with OTR-PBO coarse powder; and 3) nasal irritation in 1 subject following treatment with OC-PBO. Nasal discharge and congestion were not observed in any subjects post-dosing for any treatments.

Subject-Rated Assessment of Intranasal Irritation

No subjects reported "burning" sensations during the study.

Two subjects reported "nasal discharge, one each following OTR-PBO fine powder and OTR-PBO coarse powder.

One subject reported "facial pain/pressure" following dosing with OTR-PBO coarse.

Following administration of OTR-PBO fine powder, 2 subjects reported a "need to blow nose" and 5 reported "nasal congestion." With OTR-PBO coarse powder post-dose, 2 subjects reported "need to blow nose" and 3 subjects reported nasal congestion. One subject each reported "need to blow nose" and "nasal congestion" following treatment with OC-PBO fine powder.

According to the Sponsor, nonparametric analysis revealed no significant group differences for "need to blow nose", "runny nose", or "facial pain." The only statistical significant difference found was for "nasal congestion" scores following administration of OC-PBO fine powder compared to OTR-PBO fine powder, with an increased number of reports for the OTR-PBO fine powder. The mean (SD) score for "nasal congestion" following OTR-PBO fine powder was 1.1

Reference ID: 3192931

(1.45) indicating that the congestion was rated in the range of "very mild problem" to "moderate problem."

Reference ID: 3192931

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

/s/

JAMES M TOLLIVER
09/21/2012

SILVIA N CALDERON
09/21/2012

MICHAEL KLEIN
09/21/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilence and Epidemiology (OPE)

Date:	April 27th, 2012
To:	Robert A. Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE II) Sharon Hertz, M.D., Deputy Director, DAAAP Judy Racoosin, M.D., M.P.H., Deputy Director for Safety, DAAAP
Through:	Elizabeth Maloney, M.S., Dr.P.H. Epidemiology Team Leader Division of Epidemiology II (DEPI II) Judy Staffa, Ph.D., R.Ph. Director, Division of Epidemiology II (DEPI II)
From:	Catherine Dormitzer, Ph.D., M.P.H. Epidemiologist, DEPI II James Phillip Trinidad, M.P.H., M.S. Regulatory Review Officer, DEPI II
Subject:	Review of "A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011)"
Drug Name(s):	OxyContin® (oxycodone hydrochloride controlled-release)
Application Type/Number:	NDA# 022272
Submission Number:	N/A
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2011-0196

**This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Pharmacovigilance and Epidemiology.

Table of Contents

EXECUTIVE SUMMARY 2
1 INTRODUCTION 2
2 MATERIAL REVIEWED 3
3 RESULTS 4
3.1 Overview of Methods and Initial Findings For All Studies 4
3.1.1 Addiction Severity Indicator – Multimedia Version (ASI-MV®) and Comprehensive Health Assessment for Teens (CHAT™), National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™) 4
3.1.2 Kaiser Permanente (KP) Health System 5
3.1.3 Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program 6
3.1.4 National Poison Data System (NPDS) 6
3.1.5 National Surveys: National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), and RADARS® System College Survey (RADARS-CS) 7
3.1.6 RADARS® System Drug Diversion (DD) Program 8
3.1.7 Doctor Shopping Study 8
3.1.8 Chat Rooms Study 9
3.1.9 Kentucky Study 9
3.1.10 IMS Xponent Study 10
3.1.11 International Drug Safety Database (ARGUS) 10
3.2 General Response to DAAAP's Questions 10
3.2.1 Consistency of trends regarding desirability of OxyContin® for abuse 10
3.2.2 Consistency of trends regarding evidence of changes in abuse patterns 11
3.2.3 Consistency of trends regarding routes of abuse for OxyContin® 12
3.2.4 Maturity to support an abuse-deterrent claim 13
3.2.5 Recommended modifications necessary for the post-marketing program 13
4 CONCLUSIONS AND RECOMMENDATIONS TO SPONSORS 13
5 APPENDIX A: Acronyms and Their Definitions 17
6 APPENDIX B: References 18

EXECUTIVE SUMMARY

OxyContin® Reformulated (ORF) is a single entity (SE) extended-release (ER) opioid developed by Purdue Pharma L.P., approved on Apr 5, 2010, and marketed since Aug 2010. It has the same indication as the original OxyContin®, approved on Dec 12, 1995. ORF is indicated for "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI II), requesting a review of an interim report submitted by Purdue Pharma L.P. for ORF. Purdue submitted initial findings for 11 studies, of which eight studies had methods described in the protocols submitted to FDA on Jan 26, 2011. The four studies that are pivotal to understanding ORF's effect on OxyContin® abuse utilize the following data sources: ASI-MV® / CHAT™ NAVIPPRO™, Kaiser Permanente (KP), RADARS® System Poison Control Center Program, and the National Poison Data System (NPDS). The other seven studies may help support these studies by providing additional context on the societal, behavioral, and clinical aspects of OxyContin® abuse.

Overall, interim findings to date are generally optimistic regarding an implicit claim of route-specific abuse-deterrence. At the same time, additional follow-up post-ORF and completion of the proposed analyses are needed to appropriately evaluate the effect of the new formulation of OxyContin® on abuse and misuse. Most importantly, FDA recommends that the sponsor provide a minimum of 3 to 5 years of follow-up after the introduction of ORF for all studies to assess trends and attribute the observed decrease in abuse and misuse to changes in the formulation of OxyContin®. This timeframe is crucial to avoid missing the ability of addicts to "adjust" to the new formulation and find innovative ways to abuse it.

1 INTRODUCTION

OxyContin® Reformulated (ORF) is a single entity (SE) extended-release (ER) opioid developed by Purdue Pharma L.P., approved on Apr 5, 2010, and marketed since Aug 2010. It has the same indication as the original OxyContin®, approved on Dec 12, 1995. ORF is indicated for "management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time." Compared to the original formulation, ORF is more resistant to tampering, specifically, complete dissolution in liquids, breaking, crushing, or chewing. Purdue hypothesized that this reformulation would reduce abuse via several routes-of-administration (ROA), including injection, snorting, and oral routes that involve breaking, crushing, or chewing.

Although ORF is the first marketed opioid formulated to deter opioid drug misuse and abuse, ORF does not have an implicit or explicit labeled claim of abuse deterrence. In the Complete Response Letter dated Apr 5, 2010, FDA required that Purdue assess "the known serious risks of [ORF], in particular, whether the changes made to [OxyContin®] that are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences…addiction, overdose, and death."

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology II (DEPI II), requesting a review of an interim report submitted

Reference ID: 3123110

by Purdue Pharma L.P. for ORF. DAAAP requested that DEPI II consider the following questions in its review of the interim report:

1. Are Purdue's interim findings consistent with the initial post-marketing trends regarding
    a. desirability of OxyContin® for abuse?
    b. evidence of changes in abuse patterns from OxyContin® to oxycodone immediate-release (IR) or oxymorphone?
    c. routes of abuse for OxyContin®?
2. Are any of the findings mature enough to support an abuse-deterrent claim?
3. Are modifications necessary for this post-marketing program, and, if so, what does DEPI II recommend?

Responses to these questions are included in Section 3.2. Descriptions of all studies are found in Section 3.1; greater detail is provided for the first four (primary) studies.

Appendix A lists all the acronyms used in this review.

2 MATERIAL REVIEWED

The materials reviewed in this consult included Purdue's interim report for the post-marketing epidemiology study program, Purdue's proposed study protocols, and related communications between FDA and Purdue Pharma L.P. (1-9):

- Purdue Pharma L.P. (2011). A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011). Amended Dec 21, 2011. Submitted to DARRTS on Dec 23, 2011, for NDA# 022272
- Purdue Pharma L.P. (2011). 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 Jan 26, 2011, for NDA# 022272
- General Advice Letters sent from FDA to Purdue, dated Dec 21, 2010, Apr 5, 2011, May 19, 2011, and May 24, 2011
- Purdue's responses to FDA's General Advice Letters, dated Jan 26, 2011, and Dec 1, 2011
- An abstract titled "Initial findings on abuse rates and routes of administration following introduction of reformulated OxyContin® (oxycodone HCL controlled-release) Tablets in a sentinel surveillance system of patients in substance use treatment," presented at the 2011 PAINWeek conference held in Las Vegas, NV, on Sep 7, 2011, to Sep 10, 2011

Reference ID: 3123110

To provide context for the current review, the following previous FDA evaluations were reviewed (10-13):

- Evaluation of Preliminary Proposals and Presentations of Abuse Deterrent Studies for Extended Release OxyContin® and Embeda®, by Cynthia Kornegay, dated Nov 24, 2010
- Statistical Review and Evaluation of Oxycontin (oxycodone hydrochloride), by Bradley McEvoy, dated May 4, 2011
- Evaluation of Protocol of Abuse-Deterrence Studies, by Cynthia Kornegay, dated Mar 17, 2011
- Evaluation of Six Protocols for Abuse-Deterrence Studies on Continued Release OxyContin, by Cynthia Kornegay, dated May 13, 2011

Appendix B lists all the references cited in this review.

3 RESULTS

Purdue submitted initial findings for 11 studies, of which eight studies had methods described in the protocols submitted to FDA on Jan 26, 2011.

3.1 Overview of Methods and Initial Findings For All Studies

The four studies that are pivotal to understanding ORF's effect on OxyContin® abuse utilize the following data sources: ASI-MV® / CHAT™ NAVIPPRO™, Kaiser Permanente (KP), RADARS® System Poison Control Center Program, and National Poison Data System (NPDS). The other seven studies may help support these studies by providing additional context on the societal, behavioral, and clinical aspects of OxyContin® abuse.

3.1.1 Addiction Severity Indicator – Multimedia Version (ASI-MV®) and Comprehensive Health Assessment for Teens (CHAT™), National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™)

The objective of this study is to characterize the routes of administration (ROA) patterns and abuse associated with ORF. It is a prospective cohort study with a retrospective component. It collects data from individuals entering substance abuse treatment centers. The individuals were administered the ASI-MV® as a part of their intake process. Past 30-day abuse via specific ROA during two time periods were assessed for ORF, as well as the following comparator drugs: the original formulation of OxyContin®, oxymorphone ER and morphine ER. This study had two time periods: "pre" and "post" the introduction of ORF. The "pre" time period was from Jun 2009 to Aug 2010, and the "post" time period was from Aug 2010 through Jun 2011.

This study found that the number and proportion of respondents abusing OxyContin® per all individuals entering treatment declined (n (b) (4) pre & (b) (4) post). There was a (b) (4) reduction in overall abuse: (b) (4) via oral routes, and (b) (4) via non-oral routes. When compared to only respondents abusing any prescription opioids, the proportion of respondents that reported abuse of ORF declined 49% via all ROA, (b) (4) via oral routes, and (b) (4) via non-oral routes. The average number of days of ORF abuse decreased from (b) (4).

Reference ID: 3123110

The strength of this study is that it relies on a population that is already addicted and, thus, is a "knowledgable" population on the ROA typically used by opioid abusers. However, this is also a weakness, as this sample may or may not represent the general population, or a population that has not yet started abusing opioids, or even an abusing population that has not yet presented for treatment. Furthermore, this population of treatment centers is not a nationally representative sample and could be further strengthened with the addition of the remaining centers. To stabilize estimates, FDA also recommends that the Sponsor conduct statistical analyses of trends in abuse by year rather than quarter-year.

3.1.2 Kaiser Permanente (KP) Health System

The objective of the KP Health System Study is to estimate and compare opioid overdose and poisoning (OOP) rates in the KP Health System (Northwest, Southeast, and Northern California) before and after the introduction of ORF. Specific opioids examined in this study include OxyContin®, ER opioids (excluding OxyContin®), IR SE oxycodone, and other prescription opioids. OOP cases, which are initially identified with ICD-9-CM and ICD-10 codes in electronic medical records and state death data, will undergo validation with chart review. Similarly, opioid exposure, which is initially measured as dispensed prescriptions, will be validated with chart review for all OOP cases. Covariates used to adjust for changing population characteristics over time will include demographic and clinical characteristics. The OOP rate per each 3-, 6-, or 12-month interval is OOP cases per:

- days supply dispensed for the opioid
- unique individuals having a prescription for the opioid
- morphine equivalents dispensed among all individuals having a prescription for the opioid

Rates will be examined using a rate ratio based on three total years of rates, including 1 year after the introduction of ORF, and complemented with Poisson regression; interrupted time series analysis will be conducted based on 9.5 total years of rates, including 2.5 years after the introduction of ORF.

The interim report presented the following findings observed for KP Northwest. By Dec 2010, almost 100% of all OxyContin® dispensings used ORF. The interim report did not present findings for the proposed analysis of OOP rates. However, the reviewer calculated the crude rate of OOP cases per month for the period Jan 2010 through Jul 2010 and for the period Aug 2010 through Dec 2010, and found that the rate did not change for OxyContin® between these time periods, but increased for IR SE oxycodone and other ER opioids. Chart validation of 102 OOP cases identified with ICD codes yielded a high percentage of missing data, low positive predictive value (PPV = (b) (4) for dispensed opioids linked with OOP, and a high percentage ((b) (4) of OOP cases that were not linked to a prescription dispensed by KP. Multiple reasons may exist to explain the lack of linkage between chart-verified OOP cases and claims of opioid prescriptions dispensed within KP's data system; these include obtaining the opioid illegally, or through legitimate dispensings outside of the KP system.

Reference ID: 3123110

The interim report on the KP Health System Study does not currently demonstrate decreases in clinical indicators of OxyContin® abuse and misuse after the introduction of ORF. Data collection, chart validation, and final data analysis are required before an assessment of the results can be made.

3.1.3 Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program

The objective of this study was to estimate changes in the rates of intentional and unintentional exposure cases, assess changes in the case fatality rate, and compare the mortality rates for OxyContin® and comparator opioids before and after introduction of ORF. Cases reported to Poison Centers participating in the RADARS® System comprised the numerator data. The RADARS® System Poison Center Program obtains data from (b) (4) out of the total of (b) (4) regional United States Poison Centers. It collects data from (b) (4) states, covering over (b) (4) people in urban, suburban, and rural regions.

The comparator opioids were oxycodone IR, hydrocodone-acetaminophen, and other ER opioids (fentanyl transdermal patches plus methadone).

Key findings of this study were that, since the third quarter of 2009 (3Q2009) through 2Q2010, population rates of intentional exposure to OxyContin declined by (b) (4) in 1Q2011, and (b) (4) in 2Q2011, and that unintentional exposure rates declined by (b) (4) in 1Q2011, and (b) (4) in 2Q2011. Changes in population rates for intentional and unintentional exposures were of greater magnitude for OxyContin® than for comparator products.

One limitation of this study is that the population that is most likely to call poison control centers is most likely not the same population that abuses opioids. Secondly, data provided on a quarterly basis may be too unstable; analyses based on half-yearly or yearly data would provide a more robust estimate of reduced rates of exposures. Lastly, details were not provided on how the denominator population was obtained, e.g., were they able to only select parts of the US population that these poison control centers covered?

3.1.4 National Poison Data System (NPDS)

Similar to the RADARS® System Poison Center Program Study (see Section 3.1.3), the objective of the NPDS Study is to assess changes in exposure rates for OxyContin® and other opioids from approximately one year before to one year after the introduction of ORF. Unlike the RADARS® System Poison Center Program Study, the NPDS Study includes all 61 poison centers in the United States. The comparators to OxyContin® were heroin and SE oxycodone (excluding OxyContin®). Exposures were categorized as either intentional or unintentional. The exposure rate per quarter-year for each opioid was calculated with two different denominators:

- 100,000 U.S. population ("population-adjusted")
- 100 dispensed prescriptions (heroin excluded) ("prescription-adjusted").

Reference ID: 3123110

The main findings to date are that:

- compared to the period consisting of the third quarter of 2009 (3Q2009) through 2Q2010, the rates of all, intentional, and unintentional OxyContin® exposures per quarter-year were lower in the period 4Q2010 – 2Q2011(- (b) (4) for all exposures, - (b) (4) for intentional exposures, and - (b) (4) for unintentional exposures)
- the rates of all, intentional, and unintentional SE oxycodone exposures and heroin exposures were higher in the period 4Q2010 – 2Q2011 compared to the period 3Q2009 – 2Q2010 (+ (b) (4) + (b) (4) and + (b) (4) for SE oxycodone; + (b) (4) + (b) (4) and + (b) (4) for heroin, respectively)
- population-adjusted exposure rates followed a similar direction and magnitude of change from period 3Q2009 – 2Q2010 to period 4Q2010 – 2Q2011 as the unadjusted exposure rates
- prescription-adjusted exposure rates for OxyContin® and for SE oxycodone were lower in period 4Q2010 – 2Q2011 compared to period 3Q2009 – 2Q2010

Similar to the RADARS® System Poison Center Program study, these interim findings are suggestive of reduced OxyContin® abuse and misuse during the first year after introduction of ORF. The population-adjusted finding for SE oxycodone in this study, however, is not consistent with the lack of decrease in IR oxycodone observed in the RADARS® System Poison Center Program study. The Sponsor should explore whether different definitions of "IR oxycodone" and "SE oxycodone" account for the different results between these studies. Longer follow-up is required to examine the stability of these findings.

3.1.5 National Surveys: National Survey on Drug Use and Health (NSDUH), Monitoring the Future (MTF), and RADARS® System College Survey (RADARS-CS)

The proposed objective of this study is to assess changes in abuse patterns using NSDUH, MTF & RADARS-CS. To date, data are not available for NSDUH & MTF. The initial results from RADARS-CS have not found changes in patterns of abuse between the pre & post ORF periods.

The RADARS® System College Survey is conducted three times per year to assess nonmedical use of prescription and illegal drugs in the past 3 months among a sample of 2000 students for each survey. The sponsor did not provide sufficient information on how long after introduction of ORF have they measured and as a result it is difficult to assess the results of this survey.

Although NSDUH and MTF are drawn from nationally representative samples, the sponsor does not provide evidence that the on-line RADARS-CS is nationally representative. Although, final results from NSDUH and MTF may be informative, there will be substantial "data lag" from the time of data capture to the time it is available for analysis. That delay should be factored into the timeframe for obtaining a minimum of 3 to 5 years of follow-up after the introduction of ORF in order to assess trends and changes in abuse patterns.

Reference ID: 3123110

3.1.6 RADARS® System Drug Diversion (DD) Program

The objective of the drug diversion (DD) study is to compare the frequency of DD cases for, and average street prices of, OxyContin® and comparator opioids (fentanyl transdermal patches and methadone, IR SE oxycodone, and hydrocodone-acetaminophen) eight years before and 3.5 years after the introduction of ORF. The main findings to date are:

- a marked increase in number of DD cases for OxyContin® during the quarter-year that ORF was introduced, followed by a steep decline in DD cases
- an increase in DD cases only for IR oxycodone after the introduction of ORF
- an increased average street price for the original OxyContin® formulation after the introduction of ORF
- a lower average street price for ORF compared to original OxyContin®

Although the planned analyses have not yet been performed, the current findings are suggestive of reduced demand for OxyContin®. Alternative explanations for these findings, such as a possible decline in law enforcement activity related to the diversion of prescription opioids, are also possible. One major limitation of this study is that because the total street supply of study opioids is not (and most likely will never be) available, this study's measures of opioid desirability for abuse do not provide a complete economic context and, therefore, remain anecdotal.

3.1.7 Doctor Shopping Study

The objective of the doctor shopping study is to characterize and compare the frequency of doctor-shopping for OxyContin® and comparator opioids (fentanyl transdermal patches and methadone, IR SE oxycodone, and hydrocodone-acetaminophen) three years before and 2.5 years after the introduction of ORF. This study is a retrospective open cohort study with the cohort including Connecticut and Ohio residents whose prescriptions were reported to each state's prescription monitoring program during the study time period. The definition of doctor-shopping in this study varies and is based on the number of pharmacies and number of physicians an individual visits to fill opioid prescriptions within a specified time frame. The main findings to date are that:

- (b) (4) of all unique patients dispensed OxyContin® had used ≥3 unique pharmacies and ≥3 unique physicians
- cash payments for OxyContin® declined more for higher strengths than for lower strengths

Although the planned analyses have not yet been performed, larger declines in cash payments for higher OxyContin® strengths after the introduction of ORF may suggest a decline in doctor shopping for OxyContin®. Therefore, the sponsor suggests that including a measure of cash payments into the definition of doctor shopping will improve the definition. Including this measure could help develop a new, possibly more rigorous definition, but this measure cannot be used as a criterion for validation as it would need to be validated in a study other than the source study for the data. The sponsor has acknowledged that no gold standard for measuring doctor shopping exists.

Reference ID: 3123110

3.1.8 Chat Rooms Study

The objective of the chat rooms study is to characterize the degree (in terms of volume and specificity) and nature (including topic and content analysis) of online discussion pertaining to OxyContin® and comparator opioids two years before and 2.5 years after the introduction of ORF. The main findings to date are that:

- Posts from Nov 2010 to Sep 2011 had a higher proportion of discouraging endorsement for ORF compared to Vicodin and Dilaudid, though all three opioids have a high proportion of endorsements that were mixed (~ (b) (4) or unclear ((b) (4) to (b) (4)
- The proportion of posts about abuse of ORF via snorting or injection was lower in Jun 2011 through Sep 2011 ((b) (4) compared to Feb 2011 through May 2011 ((b) (4)
- The overall frequency of determined tamperers who claimed to abuse ORF by routes that require tampering was low; for example, (b) (4)) of authors who posted during Aug 2010 to Feb 2011 claimed to abuse ORF by means of injection.

The main strength of this study is hypothesis generation regarding the possible methods of extraction. Inference about the desirability of ORF abuse and ability to abuse ORF via routes that require tampering is limited. For example, while a reduction in the proportion of posts about abuse and extraction of ORF could stem from less demand for ORF abuse via routes requiring tampering, other reasons may exist (such as previous posts of successful extraction reducing the need for future posts).

3.1.9 Kentucky Study

The objective of this study was to identify methods of preparation and ROA for pharmaceutical and illegal opioids. It is a longitudinal sample of 200 self-reported OxyContin® abusers in a cohort of individuals in eastern Kentucky who had abused the original formulation of OxyContin® prior to the introduction of ORF.

The prevalence of abuse of pharmaceutical and illegal drugs in the month before introduction of ORF was compared with the post-ORF period. Despite the lack of expected availability of original OxyContin® in the post-ORF period, a similar proportion of the sample reported abuse of original OxyContin® in the post-ORF period (b) (4)) as in the period before ORF was introduced (b) (4) Only (b) (4) reported use of ORF in the past thirty days at the time of the post-ORF interview.

These findings are premature and based on anecdotal data obtained from a convenience sample recruited through community outreach and "snowball sampling"[1], and as a result may not be generalizable. In addition, the sample size is not sufficient for multivariate statistical analyses. FDA recommends that the sponsor should provide a clear and

[1] Snowball sampling is a non-probability sampling technique whereby existing study subjects recruit future subjects from among their acquaintances. It is used when studying a population that is difficult to reach (14; 15)

Reference ID: 3123110

detailed explanation of how the study results will be used to enhance safety surveillance of ORF.

3.1.10 IMS Xponent Study

The objective of the IMS Xponent study is to assess changes in prescribing of OxyContin® and opioid comparators one year before and one year after the introduction of ORF. This study focuses on differences in prescribing patterns among various OxyContin® strengths as well as Abuse and Diversion Detection (ADD) prescribers, described as prescribers possibly associated with OxyContin® abuse or diversion-related activities. The main findings to date are that a slight decline ([(b) (4)] in OxyContin® prescriptions was observed nationwide after the introduction of ORF, with the greatest declines among ADD prescribers ([(b) (4)] for 40 and 80 mg strengths ([(b) (4)] and [(b) (4)] respectively), and cash payments ([(b) (4)] These interim findings are suggestive of reduced demand for ORF compared to original OxyContin®. FDA recommends that the sponsor determine whether the findings for ADD prescribers could be explained by an unstable number of prescribers after the introduction of ORF. On a related note, the large spike in DD cases in the quarter-year that ORF was introduced could explain the reduction in OxyContin® prescriptions among ADD prescribers (see Section 3.1.6). Specifically, this large spike may have resulted in a reduction in the number of ADD prescribers (for example, due to arrests and/or revocation of medical licenses) and, subsequently, a reduction in OxyContin® prescriptions from these prescribers.

3.1.11 International Drug Safety Database (ARGUS)

This study utilizes Purdue's Post Market International Drug Safety Database (ARGUS). The objective of this analysis was to review and analyze the OxyContin post-marketing cases reported to Purdue that were associated with drug abuse, intentional drug misuse, overdose, and medication errors involving original OxyContin® versus ORF. There was a 62% decline in abuse-related adverse events, and the reporting rate declined from 30 to 12 per 100,000 prescriptions. Since these data represent passive surveillance, these changes may be the result of other well-known factors that affect reporting (16). As a result, reductions in reports may not be due to changes in the formulation and could represent other unknown factors.

3.2 General Response to DAAAP's Questions

3.2.1 Consistency of trends regarding desirability of OxyContin® for abuse

The Reviewers believe that eight of these 11 studies, when completed, could provide insight on trends of the desirability of OxyContin® for abuse. Results from the following three studies suggest reduced desirability of OxyContin®, and were consistent with the PAINWeek abstract regarding an overall reduction of OxyContin® for abuse:

- Addiction Severity Indicator – Multimedia Version (ASI-MV®) and Comprehensive Health Assessment for Teens (CHAT™) National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™) Study. Specifically, the number of respondents abusing OxyContin® per all individuals entering treatment declined: [(b) (4)] overall, [(b) (4)] via oral routes, and [(b) (4)] via non-oral routes. The number of respondents abusing OxyContin® per individuals abusing any prescription opioid declined 49% overall, [(b) (4)] via oral routes, and

Reference ID: 3123110

(b) (4) via non-oral routes. The average number of days of OxyContin® abuse decreased from eleven days to seven days.

- National Poison Data System (NPDS) Study. Specifically, this study showed a (b) (4) reduction in the average number of intentional-abuse OxyContin® exposures per quarter-year after the introduction of ORF.
- Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Drug Diversion (DD) Program Study. Specifically, the possible metrics of desirability of OxyContin® for abuse (DD cases per 100,000 population, DD cases per unique individuals dispensed OxyContin®, and the average street price of OxyContin®) all decreased after the introduction of ORF.

Results from the following two studies had mixed results regarding a reduction in the desirability of OxyContin® for abuse, as suggested by the PAINWeek abstract:

- Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program Study. Specifically, intentional exposure population rates declined by (b) (4) in 1Q2011 & (b) (4) in 2Q2011; unintentional exposure rates declined by (b) (4) in 1Q2011 and (b) (4) in 2Q2011; and the changes in population rates for intentional and unintentional exposures were of greater magnitude for OxyContin® than for comparator products.
- Chat rooms study. Specifically, the proportion of internet posts endorsing OxyContin® for abuse decreased slightly, but proportion of internet posts with discouraging or mixed endorsement also decreased slightly, while the proportion of internet posts with an unclear endorsement greatly increased.

The interim report did not report any results for the following studies that, if conducted as initially proposed, could provide insight on desirability of OxyContin® for abuse, as suggested by the PAINWeek abstract:

- Kaiser Permanente (KP) Health System Study
- National Surveys Study
- The doctor shopping study

3.2.2 Consistency of trends regarding evidence of changes in abuse patterns

The PAINWeek abstract did not specifically mention oxycodone IR and oxymorphone. However, the abstract suggests that since the proportion of abuse for OxyContin® decreased among respondents who abused any prescription opioid, the proportion of abuse for other opioids increased. The Reviewers believe that six of the studies, when completed, could answer DAAAP's question regarding consistency of trends in changing abuse patterns from OxyContin® to either oxycodone IR, or oxymorphone, or both. Results from the following three studies showed a reduction in abuse in Oxycontin® with a concomitant increase in abuse in oxycodone IR:

- Kaiser Permanente (KP) Health System Study. Specifically, during 2010, overdose and poisonings per month decreased by (b) (4) for OxyContin®, but increased by (b) (4) for SE IR oxycodone, after the introduction of ORF.

Reference ID: 3123110

- RADARS® System Drug Diversion (DD) Program Study. Specifically, the possible metrics of OxyContin® abuse (DD cases per 100,000 population, DD cases per unique individuals dispensed OxyContin®, and the average street price of OxyContin®) all decreased after the introduction of ORF, but generally increased for IR oxycodone
- The Kentucky Study. Specifically, in the post-ORF assessment, (b) (4) reported abuse of the original OxyContin formulation and (b) (4) reported abuse of other oxycodone products, as compared to (b) (4) for ORF.

Results from the following two studies showed a reduction in abuse in Oxycontin® with a concomitant increase in abuse in oxymorphone:

- Addiction Severity Indicator – Multimedia Version (ASI-MV®) and Comprehensive Health Assessment for Teens (CHAT™) National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™) study. Specifically, among all assessed patients, the abuse rates for ER oxymorphone more than doubled from (b) (4) cases per 100 (relative change = (b) (4); 95% CI = (b) (4) The rates of abuse of ER oxymorphone among the patients who were identified as prescription opioid abusers increased (b) (4) in the period following introduction of ORF, from (b) (4) per 100 individuals who abused prescription opioids.
- The Kentucky Study. Specifically, there were significant increases in abuse of Opana® ER (from (b) (4) during in the month before introduction of ORF and in the month prior to interview in the post-ORF period.

3.2.3 Consistency of trends regarding routes of abuse for OxyContin®

Results from the following two studies were consistent with the PAINWeek abstract regarding a shift in abuse from non-oral routes to oral routes:

- Addiction Severity Indicator – Multimedia Version (ASI-MV®) and Comprehensive Health Assessment for Teens (CHAT™) National Addiction Vigilance Intervention and Prevention Program (NAVIPPRO™) Study. Specifically, the number of individuals abusing OxyContin per 100 patients entering substance treatment declined (b) (4) overall following ORF introduction: (b) (4) through oral routes and (b) (4) through non-oral routes.
- Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program Study. Specifically preliminary results indicate that there is evidence of a decline in exposures through injection and inhalation routes following the introduction of ORF. It is based, however, on a small number of exposures via non-oral routes.

The interim report did not include any results for the Kaiser Permanente (KP) Health System Study that, if conducted as initially proposed, could provide insight on shifts in abuse patterns between non-oral routes and oral routes.

Reference ID: 3123110

3.2.4 Maturity to support an abuse-deterrent claim

The data seem generally optimistic regarding an implicit claim of route-specific abuse deterrence. However, the analyses presented to date are descriptive only, so no conclusions can be drawn. While data collection was complete for some studies, no formal analyses, as described in the study protocols, have been completed for any of those studies. For other studies, the data collection continues through Dec 2012 or Jan 2013 (providing 2.5 years of follow-up since the introduction of ORF); this length of follow-up is less than the 3 - 5 years of minimum follow-up that was previously suggested (10). The reviewers believe that 3 - 5 years of follow-up data are required to assess trends. As none of the studies reviewed have completed the minimum follow-up, or reported formal statistical analyses, none are mature enough to support an abuse-deterrent claim at this time.

3.2.5 Recommended modifications necessary for the post-marketing program

This reviewers recommend one major modification and several minor modifications to Purdue's post-marketing epidemiology study program. The major modification is to have the combination product oxycodone-acetaminophen added as a comparator for studies based on the following data sources: ASI-MV® / CHAT™ NAVIPPRO™, KP Health System, RADARS® System Poison Center Program, and NPDS. Though oxycodone-acetaminophen will have a different pattern of drug utilization due to the presence of acetaminophen, the reviewers recommend comparing ORF to oxycodone-acetaminophen for the following reasons:

- Abuse deterrent products could include products containing a component that produces an adverse effect if the product is not taken as indicated (17).
- Purdue stated that hydrocodone-acetaminophen was a suitable comparator to ORF because acetaminophen causes adverse effects (specifically, irritation) when used via injection or inhalation, and therefore, switching from ORF to hydrocodone-acetaminophen for abuse via injection or inhalation is not expected to occur.

Historical trends of OxyContin® abuse could provide an upper estimate of OxyContin® abuse via injection and snorting, and historical and prospective data of oxycodone-acetaminophen abuse could suggest a possible lower estimate. Additionally, whenever possible, the studies should use the same opioid comparators.

For brevity, minor modifications to the design and analysis of Purdue's post-marketing epidemiology study program are listed in Section 4, Conclusions and Recommendations to Sponsors. Whenever applicable, Section 4 also suggests use of oxycodone-acetaminophen as a comparator.

4 CONCLUSIONS AND RECOMMENDATIONS TO SPONSORS

Overall, interim findings to date are generally optimistic regarding an implicit claim of route-specific abuse-deterrence. At the same time, <u>additional follow-up post-ORF and completion of the proposed analyses</u> are needed to appropriately evaluate the effect of the new formulation of OxyContin® on abuse and misuse. FDA recommends that the sponsor:

Reference ID: 3123110

- Provide a minimum of 3 to 5 years of follow-up after the introduction of ORF for all studies to assess trends and attribute the observed decreased in abuse and misuse to changes in the formulation of OxyContin®. This timeframe is crucial to avoid missing the ability of addicts to "adjust" to the new formulation and find innovative ways to abuse it
- Add the combination product oxycodone-acetaminophen as a comparator for studies conducted using the following data sources: ASI-MV® / CHAT™ NAVIPPRO™, KP Health System, RADARS® System Poison Center Program, RADARS® system Drug Diversion Program, the doctor shopping study, and the NPDS Study
- Conduct statistical analyses of trends in abuse by year rather than quarter-year for the NAVIPPRO™ Study and RADARS® System Poison Center Program Study. This should help to stabilize the estimates.
- Address the following concerns in the KP Health System Study:
    - Include ICD codes E935.x and Y45.0 when determining the accuracy of electronic medical record-identified type 2 cases of opioid overdose and poisonings (OOP)
    - Describe how the classifications of certainty of opioid involvement ('definite,' 'probable,' and 'possible') differ; describe if and how the planned analyses will incorporate these classifications into the measurement of OOP cases
    - Resolve the discrepancy in confirmed type 1 cases; specifically, the narrative in Section 4.2.3 states there were 15/27 type 1 cases while Table 12 calculates 22/27 type 1 cases (based on definite + probable + possible + polydrug cases)
- Address the following concerns in the RADARS® System Poison Center Program Study:
    - Provide a table describing how RADARS® System Poison Center Program data compares with that from the universe of 61 poison centers
- Address the following concerns in the National Poison Data System (NPDS) Study:
    - Compare OxyContin® exposure to the same comparators (oxycodone-acetaminophen, IR oxycodone, hydrocodone-acetaminophen, and fentanyl and methadone) as the RADARS® System Poison Center Program Study
    - Present results for the opioid comparators similar to results shown for OxyContin® in Table 50. Collapsing the unintentional exposure categories *bite/sting*, *food poisoning*, *occupational*, *unknown*, and *environmental* may be reasonable if the other comparators show similar small number of exposure events in these categories.
    - Use regression analysis (similar to analysis from the RADARS® System Poison Center Program Study) to characterize whether the trend of

Reference ID: 3123110

exposure (and exposure rates) measured by NPDS changes after the introduction of ORF

  - Move the analysis of percent change in IR oxycodone prescriptions compared to OxyContin®, using dispensed prescription data stratified by state, from the NPDS study to Supplemental Study 9 since such an analysis would be more appropriate in addressing changes in drug utilization; also, consider other strengths and opioids, as well as standardizing the opioids as morphine equivalents
  - Clarify whether "IR oxycodone" refers to "IR SE oxycodone" or both "IR SE and combination oxycodone products"; this clarification also applies to other studies where applicable

- Address the following concerns about the RADARS System College Survey:
  - Describe how this sample was derived and how this population compares with college students on a national level
  - Incorporate longer time periods (half-yearly, or yearly) into the analysis of the college survey; every 3 months is too short. Power calculations for the college survey should also be provided.

- Address the following concerns about the RADARS® System Drug Diversion Program:
  - Adjust the opioid street prices for inflation and (if possible) geographic differences

- Address the following concerns about the doctor shopping study:
  - Describe whether the prescription monitoring programs capture medications prescribed, prescriptions dispensed, or both
  - Compare doctor shopping for OxyContin® to a non-opiate negative control (see the study by Cepeda et al. (18))
  - (If possible) identify a criterion to be used in concurrent or predictive validation of doctor shopping definitions
  - For the primary analysis, use the definitions of doctor shopping specified in the protocol (pgs. 104-105, specifically, the *single-opioid product doctor shopping* definition and the *mixed-opioid product doctor shopping* definition) without the addition of measurements of cash payments (or any other deviations from the original definitions); use of the original definitions in the primary analyses will allow this study to be better compared to the studies by Pradel et al. and Katz et al. (19; 20)
  - Only use doctor shopping definitions that deviate from the proposed definitions in sensitivity analyses; deviations may include incorporating measurements of cash payments, history of opioid prescriptions, age, and sex

Reference ID: 3123110

- Address the following concerns about the chat rooms study:
    - Provide a description of each of the websites used in the study, including: names of the websites, number of posts per time interval (for example, per month) over the study period, number of authors per time interval, and number of posts per author
    - Provide an explanation for the use of the comparators Vicodin and Dilaudid
    - Use the same comparators as the other studies
    - Clarify the difference between the endorsement classifications *mixed* and *unclear*; provide an explanation for why the proportion of *mixed* and *unclear* endorsement is prevalent among all comparators
- Address the following concerns about the ARGUS Study:
    - In addition to analyzing post-marketing cases associated with drug abuse, intentional drug misuse, overdose, and medication errors involving original OxyContin® versus ORF using the number of prescriptions dispensed as the denominator (e.g. "reporting rates"), use number of patients and number of pills dispensed as alternate denominators
- Address the following concerns about the Kentucky study:
    - Provide a clear and detailed explanation of how the results from the Kentucky study will be used to enhance safety surveillance of ORF
- Address the following concerns about the IMS Xponent study:
    - Determine whether the findings from the IMS Xponent Study for ADD prescribers could be explained by an unstable number of prescribers after the introduction of ORF
- Explore whether the definitions of "IR oxycodone" and "SE oxycodone" account for the different results obtained from the NPDS Study and the RADARS System Poison Center Program Study

Reference ID: 3123110

5 APPENDIX A: ACRONYMS AND THEIR DEFINITIONS

Table 1: List of Acronyms

Acronym	Definition
#QYYYY (such as 1Q2011)	First / second / third / fourth quarter of year YYYY
ADD	Abuse and Diversion Detection
ARGUS	International Drug Safety Database
ASI-MV®	Addiction Severity Indicator – Multimedia Version
CHAT™	Comprehensive Health Assessment for Teens
DAAAP	Division of Anesthesia, Analgesia, and Addiction Products
DD	Drug diversion
DEPI II	Division of Epidemiology II
ER	Extended-release
ICD-10	International Classification of Diseases, 10th Revision
ICD-9-CM	International Classification of Diseases, 9th Revision – Clinical Modification
IR	Immediate-release
KP	Kaiser Permanente
MTF	Monitoring the Future
NAVIPPRO™	National Addiction Vigilance Intervention and Prevention Program
NPDS	National Poison Data System
NSDUH	National Survey on Drug Use and Health
OOP	Opioid overdose and poisoning
ORF	Reformulated OxyContin®
PPV	Positive predictive value
RADARS®	Researched Abuse Diversion and Addiction-Related Surveillance (RADARS®) System
RADARS-CS	RADARS® System College Survey
ROA	Routes of administration
SE	Single entity

Reference ID: 3123110

6 APPENDIX B: REFERENCES

1. Purdue Pharma L.P. (2012). *A Summary of the Findings of the Post-Marketing Epidemiology Study Program to Detect Changes in Patterns of Abuse and Misuse and their Consequences: Addiction, Overdose and Death (as of October 15, 2011)*. Amended Dec 21, 2011. Submitted to DARRTS on Dec 23, 2011, for NDA #022272.

2. Purdue Pharma L.P. (2011). *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 Jan 26, 2011, for NDA #022272.

3. Rappaport, B. A. & Hertz, S. H. (2010). Advice/Information Request. FDA/CDER/OND II. Submitted to DARRTS on Dec 21, 2010, for NDA #022272.

4. Rappaport, B. A. & Hertz, S. H. (2011). General Advice Letter. FDA/CDER/OND II. Submitted to DARRTS on Apr 5, 2011, for NDA #022272 and IND# 029038.

5. Rappaport, B. A. & Hertz, S. H. (2011). General Advice Letter. FDA/CDER/OND II. Submitted to DARRTS on May 19, 2011, for NDA #022272 and IND# 029038.

6. Rappaport, B. A. & Hertz, S. H. (2011). General Advice Letter. FDA/CDER/OND II. Submitted to DARRTS on May 24, 2011, for NDA #022272 and IND# 029038.

7. Purdue Pharma L.P. (2011). *Purdue's Response to FDA's Information/Advice Letter (dated December 21, 2010) on Purdue's proposed Epidemiology Study Program as presented at the October DAAP Advisory Committee meeting*. Submitted to DARRTS on Jan 26, 2011, for NDA #022272.

8. Purdue Pharma L.P. (2011). *Purdue's Response to FDA's General Advice Letters (dated April 5, 2011 and May 19, 2011) on the Protocols for Purdue's OxyContin Epidemiology Study Program*. Submitted to DARRTS on Dec 1, 2011, for NDA #022272.

9. Cassidy, T. A., Coplan, P., Black, R. A., Chilcoat, H., Budman, S. H., & Butler, S. F. (2011). Initial findings on abuse rates and routes of administration following introduction of reformulated OxyContin® (oxycodone HCL controlled-release) Tablets in a sentinel surveillance system of patients in substance use treatment. In *PAINWeek*, held in Las Vegas, NV: Sep 7, 2011. Submitted to DARRTS on Aug 4, 2011, for NDA# 022272.

Reference ID: 3123110

10. Kornegay, C. (2010). *Evaluation of Preliminary Proposals and Presentations of Abuse Deterrent Studies for extended release OxyContin® and Embeda®.* FDA/CDER/OSE. Submitted to DARRTS on Dec 9, 2010, for NDA #022272 and NDA #022321.

11. McEvoy, B. (2011). *Statistical Review and Evaluation of OxyContin (oxycodone hydrochloride)*. Statistical Review and Evaluation: Clinical Studies. FDA/CDER/OTS/OB. Submitted to DARRTS on May 4, 2011, for NDA #022272.

12. Kornegay, C. (2011). *Evaluation of Protocol for Abuse-Deterrence Studies*. Epidemiologist Study Protocol Review. FDA/CDER/OSE. Submitted to DARRTS on Mar 18, 2011, for NDA #022272.

13. Kornegay, C. (2011). *Evaluation of Six Protocols for Abuse-Deterrence Studies on Continued Release OxyContin*. Epidemiologist Study Protocol Review. FDA/CDER/OSE. Submitted to DARRTS on May 13, 2011, for NDA #022272.

14. Biernacki, P. & Waldorf, D. (1981). Snowball Sampling - Problems and Techniques of Chain Referral Sampling. *Sociological Methods & Research, 10,* 141-163.

15. Magnani, R., Sabin, K., Saidel, T., & Heckathorn, D. (2005). Review of sampling hard-to-reach and hidden populations for HIV surveillance. *AIDS (London, England), 19 Suppl 2,* S67-S72.

16. Strom, B. L. (2005). *Pharmacoepidemiology*. (4th ed.) Etobicoke, Ontario, Canada: John Wiley & Sons, Canada Ltd.

17. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, October 21 and 22, 2010. (2010). FDA/CDER.

18. Cepeda, M. S., Fife, D., Chow, W., Mastrogiovanni, G., & Henderson, S. C. (2012). Assessing Opioid Shopping Behaviour: A Large Cohort Study from a Medication Dispensing Database in the US. *Drug safety : an international journal of medical toxicology and drug experience, 35,* 325-334.

19. Pradel, V., Thirion, X., Ronfle, E., Masut, A., Micallef, J., & Begaud, B. (2004). Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. *Pharmacoepidemiology and drug safety, 13,* 473-481.

Reference ID: 3123110

20. Katz, N., Panas, L., Kim, M., Audet, A. D., Bilansky, A., Eadie, J. et al. (2010). Usefulness of prescription monitoring programs for surveillance--analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006. *Pharmacoepidemiology and drug safety, 19,* 115-123.

Reference ID: 3123110

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

/s/

JAMES TRINIDAD
04/27/2012

CATHERINE M DORMITZER
04/27/2012

JUDY A STAFFA
04/27/2012

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 4, 2009

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: NDA 22-272 – OxyContin (oxycodone hydrochloride) Controlled-Release Tablets (Reformulated OxyContin). 10, 15, 20, 30, 40, 60 and 80 mg capsules

Indication: Relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

Company: Purdue Pharma L.P.

Submission: NDA 22-272 is located in the EDR. CSS has reviewed the following documents found in Module 3.2.P of the Application and submitted in March, 2009: "*Comprehensive In Vitro Testing of the Controlled-Release Properties of New OCR Tablets After Physical and Chemical Manipulation - Summary Report"; "Comprehensive in Vitro Testing of the Controlled-Release Properties of New OCR Tablets After Physical and Chemical Manipulation - Complete Dataset Appendix"; " Evaluation of the Resistance to Physical and Chemical Manipulation of Oxycodone HCl (10, 15, 20, 30, 40, 60 and 80 mg) TR Tablets Compared to Currently Marketed OxyContin (10, 15, 20, 30, 40, 60 and 80 mg)"; " Protocol for Creating Particle Size Fractions by Crushing and Milling Extended Release Oxycodone HCl Tablets - OxTR In Vitro Testing Plan - Experiments 2a, b and 5a, b, c"; Protocol TTP-PMP-M0043.00 - "Simple Extraction: pH-Dependent API Release Study for Extended Release Oxycodone HCl Tablets"; " Protocol for Smoking (Inhalation) Testing of Physically Manipulated Extended Release Tablets Containing Oxycodone HCl"; "Validation Protocol for Simple Extraction Testing of Physically Manipulated Extended Release Tablets Containing Oxycodone HCl'.*

This review provides conclusions and recommendations from CSS to the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) regarding the abuse potential and deterrent properties of reformulated OxyContin Controlled-Release Tablets. This is in response to a consult sent to CSS from DAARP.

Background:
In November, 2007, Purdue Pharma L.P. submitted NDA 22-272 for a reformulation of OxyContin. This was the subject of a May 5, 2008 Advisory Committee meeting. Sponsor received an October 3, 2008 Complete Response Letter requesting additional physicochemical testing of the reformulated tablets. In response to this letter, Sponsor submitted an updated application on March 27, 2009, provided detailed information on in vitro studies conducted to evaluate the tamper-resistant characteristics of the reformulated tablets, including the 60 and 80 mg strengths, with comparison to the tamper resistant characteristics of the currently available OxyContin.

Reformulated OxyContin controlled-release tablets contain 10, 15, 20, 30, 40, 60 and 80 mg oxycodone hydrochloride (HCl) intended for twice daily dosing (q12h) for treatment of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The reformulated tablets are formulated using an eroding matrix with polyethylene oxide (PEO) as a release-control polymer. The rate of oxycodone release is controlled by (b) (4) which the Sponsor asserts makes the tablets resistant to (b) (4) related increases in drug release, and more resistant to compromise by some common forms of manipulation (crushing, simple extraction).

Data[1] from the National Survey on Drug Use and Health (NSDUH), the Drug Abuse Warning Network (DAWN) and the Treatment Episode Data Set (TEDS) show that the nonmedical use or abuse of prescription opioids is a significant problem in the United States. This has resulted in increased rates of opioid-related mortality and admissions to hospital emergency departments and publicly funded substance abuse treatment facilities. Information on routes of administration involved in the nonmedical use or abuse of prescription opioids is limited. A few literature articles report that oral administration is the main route by which prescription oxycodone products are used nonmedically, with a smaller percentage of individuals abusing oxycodone products by injection or other routes of administration[2]. Extended release formulations containing large amounts of opioids may undergo tampering by crushing or dissolution resulting in the release of large doses of drug. The tampered formulations can then be ingested, snorted, smoked or intravenously administered. A review conducted by the Sponsor specifically pertaining to OxyContin shows that the oral route is the most commonly used route for the misuse

[1] Substance Abuse Mental Health Services Administration (SAMHSA) data bases
[2] Havens et al. (2007). Drug and Alcohol Dependence, 87: 98-102 and Rees Davis and Johnson (2008). Drug and Alcohol Dependence, 92: 267-276 and Butler et al (2008). Pharmacoepidemiology and Drug Safety, in press.

and abuse of OxyContin.[3] The review noted, however, that more experienced abusers report injecting or inhaling crushed OxyContin tablets. The percentage of OxyContin abusers who used parenteral routes is low as compared to the number of abusers who use the oral route.

Conclusions[4]:

1. This application covers the reformulation of all dosage strengths. Detailed in vitro testing to characterize tamper-resistant properties was conducted on all dosage strengths of reformulated OxyContin.

2. As a product that is bioequivalent to OxyContin, all oxycodone blood levels produced by the intact reformulated product are expected to be the same as those produced by OxyContin at all points in time after oral administration. Thus, oral abuse of the intact new formulation is not deterred.

3. The proposed reformulation of OxyContin may provide enhanced protection over that provided by the currently available OxyContin for the intended population against dose dumping when tablets are accidentally crushed or chewed.

4. The Sponsor conducted an extensive number of *in vitro* studies in order to characterize the tamper-resistant properties of the various dosage strengths of reformulated OxyContin tablets. Collectively these studies show:

   - Reformulated OxyContin tablets are considerably more difficult to chew or crush compared to currently available OxyContin. A coffee bean or laboratory grinder is required to produce a small particle size powder. By contrast, using two stainless steel spoons or using a mortar and pestle are sufficient to reduce currently available OxyContin to a fine powder.

   - The greater difficulty in crushing or chewing the reformulated OxyContin product gives the product an enhanced protective advantage over that of currently available OxyContin with regard to the immediate release of a high dose of oxycodone (dose dumping).

   - Water is effective in extracting the oxycodone HCl from crushed reformulated OxyContin as well as from the currently available OxyContin. In general, the reformulated product should be viewed as a limited improvement over the currently available OxyContin. Crushing of the product or increasing water temperature result in increased extraction of

[3] "Routes of Administration Associated with the Nonmedical Use and Abuse of OxyContin®: A Review" by Meredith Smith.

4 CSS acknowledges the lack of general guidelines for studying and evaluating the “tamper resistant” or “abuse deterrent” features of a drug product that could include consistent advice on test procedures including solvents and extraction conditions to be used and the input of law enforcement experts and drug abuse researchers.

oxycodone HCl. For example, approximately (b) (4) of the oxycodone HCl in reformulated OxyContin is extracted at (b) (4) in a small volume (b) (4) of water at room temperature (b) (4) from finely crushed (b) (4) µm) reformulated OxyContin tablets (b) (4) This fine powder could be achieved using a (b) (4) grinder for (b) (4). This percentage of extracted API translates in (b) (4) of oxycodone extracted from ground reformulated 40 mg, 60 mg and 80 mg oxycodone tablets at (b) (4) respectively. For purposes of comparison, within (b) (4) of oxycodone HCl is extracted in (b) (4) from crushed, currently available OxyContin.

- Water is also effective in extracting oxycodone HCl from intact tablets of reformulated OxyContin. Sponsor showed that in (b) (4) of oxycodone HCl could be extracted from intact reformulated tablets (Band 1) within one hour. Thus, this simple procedure can afford clinically significant amounts of oxycodone from high strengths intact tablets of the reformulated product without effort.

- (b) (4) are effective solvents for extracting oxycodone HCl from reformulated OxyContin tablets without using extreme procedures. Grinding up the tablets to produce powders of different particle size compromises the release resistant properties of the tablets, and results in increased percentages of oxycodone HCl release, particularly within three hours of extraction. The percentages of the active pharmaceutical ingredient (API) released under various conditions and at the early time points from reformulated OxyContin is lower than that extracted from the currently available OxyContin, thereby providing some, but limited advantage to the reformulated product. Increasing solvent temperature usually, but not always, increases the extent of oxycodone HCl extraction at given time points. The effect of temperature is more relevant when using intact reformulated tablets.

- Buffered solutions of pH 1, pH 3 and pH 8 are effective solvents in extracting oxycodone HCl from intact and powdered samples of reformulated Oxycontin and from crushed currently available crushed OxyContin. Increasing the pH to 10 reduces the percentage oxycodone HCl extracted from both intact and crushed products. Over the first two hours, the extent of extraction is greater from crushed currently available OxyContin, as compared to the extent of extraction either from intact or powdered samples of reformulated OxyContin.

- Due to the presence of PEO, it is difficult to use reformulated OxyContin tablets to prepare an aqueous solution suitable of intravenous (i.v.) injection. By contrast, low volume, highly potent, and aqueous solutions of oxycodone for i.v. use can be prepared from currently available OxyContin.

- Both reformulated OxyContin and currently available OxyContin are not likely to be abused by inhalation because the temperature for vaporization of oxycodone HCl is close to the temperature at which oxycodone HCl decomposes. Conversion of the hydrochloride salt to the free base is necessary for preparation of an inhalable product.

- Oxycodone base is not soluble in alkaline solutions and can be separated by (b) (4) However, (b) (4) of oxycodone base using an (b) (4) procedure, "free basing," followed by filtration proved to be time consuming and inefficient due to the presence of PEO and high viscosity of the solution. Obtaining oxycodone free base from reformulated OxyContin took three times as long (more than two hours) as obtaining the free base from currently available OxyContin.

- (b) (4) as the organic solvent is of limited effectiveness in extracting oxycodone base from an alkaline solution (free-basing procedure) from either the reformulated or currently available OxyContin product. The Sponsor did not evaluate the use of (b) (4)

CSS Review:

<u>Mechanical Fractionation of Tablets</u>

The Sponsor identified methods to mechanically fractionate reformulated 80 mg OxyContin tablets using readily available household devices. Both the time and effort required for such fractionation was compared to the time and effort required to fractionate 80 mg of the currently marketed OxyContin tablets. (b) (4) were used to generate discrete ranges of particle sizes. Particle sizes were divided into the following seven particle size Bands:

Band 1 (b) (4)
Band 2
Band 3
Band 4
Band 5
Band 6
Band 7
(b) (4)

These distinct Bands represent the full particle size range likely to be used for attaining preparation for misuse, accidental or otherwise, by the general population. Household tools evaluated for fractionating tablets included stainless steel kitchen tablespoons,

(b) (4) Not all of these tools were evaluated for crushing currently available OxyContin.

Currently available OxyContin tablets were readily crushed using household tools. A simplistic tool, specifically two stainless steel tablespoons, readily crushed these tablets into a powder, as did a manual pill crusher, hammer, ceramic mortar and pestle, fine grater and coffee bean grinder (b) (4)). A mortar and pestle was very effective in rapidly (within seconds) rendering currently available OxyContin into a powder, (b) (4)

Crushing reformulated OxyContin tablets proved much more difficult compared to crushing currently available OxyContin tablets. Despite multiple attempts, the following devices were ineffective in reducing the reformulated tablets to particles or tablet fragments: (b) (4)

Tools that were effective in fractionating the core material of reformulated OxyContin tablets included a (b) (4)

Sponsor also looked at the effects of (b) (4)

Extraction in Water

Studies were conducted by an independent contractor to examine the use of water as a solvent to extract oxycodone HCl from reformulated OxyContin and from the current formulation of OxyContin. Extraction was evaluated for Bands 1, 2, 3, 4, 5 and 6 of the all strengths of reformulated OxyContin, Band 7 (b) (4)), and crushed and current 10, 40 and 80 mg OxyContin tablet. Bands 2, 4, 5 and 6 were produced using a (b) (4)

(b) (4)

15 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

----

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

/s/

JAMES M TOLLIVER
09/04/2009

SILVIA N CALDERON
09/04/2009

MICHAEL KLEIN
09/04/2009