CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272Orig1s014

SUMMARY REVIEW

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

To: **Douglas C. Throckmorton, MD**
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

From: **Janet Woodcock, MD**
Director
CDER, FDA

Subject: **Abuse-Deterrent Properties of Reformulated OxyContin (oxycodone hydrochloride) Extended-Release Tablets**

Date: **April 16, 2013**

I have reviewed your memorandum (including the appended data summary tables) regarding (1) the CDER review of the labeling supplement for reformulated OxyContin (oxycodone hydrochloride) extended-release tablets (OCR) (NDA 22-272), including your recommendation about whether the labeling should be revised to include language describing abuse-deterrent properties of the new formulation, and (2) whether Purdue's original formulation of OxyContin (oxycodone hydrochloride) extended-release tablets (OC) (NDA 20-533) should be determined to be withdrawn for reasons of safety or effectiveness.

I concur with your analyses and recommendations and I conclude that:

1. The labeling for OCR should be revised to include appropriate language describing the abuse-deterrent properties of the new formulation (along with relevant caveats); and

2. OC was withdrawn for reasons of safety or effectiveness.

Thank you for your leadership in this complex, multidisciplinary effort.

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/s/

LISA E BASHAM
04/16/2013
Entered into DARRTS on behalf of Dr. Janet Woodcock

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS
HFD-170, 10903 New Hampshire Avenue, Silver Spring, MD, 20993

Division Director Review, Addendum

Drug Name: OxyContin Tablets, Reformulated (ORF)
Sponsor: Purdue Pharma
Date of Review: April 15, 2013
Division Director: Bob A. Rappaport, M.D.

In my capacity as Division Director of the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), I am writing this addendum to clarify the summary conclusions in my review dated February 6, 2013, regarding Purdue's reformulated OxyContin (ORF) and potential abuse-deterrent properties.

As noted in my original review, the appended DAAAP medical officer review was completed by Dr. Pamela Horn with oversight from Dr. Sharon Hertz, in November of 2012, prior to Dr. Horn's going on extended leave of absence. That review evaluated in vitro, pharmacokinetic and "drug liking" pharmacodynamic, clinical, and postmarketing data. The review was not filed at that time as Drs. Horn and Hertz were waiting for the epidemiology study reviews to be completed by another office within CDER, the Division of Epidemiology in the Office of Surveillance and Epidemiology (OSE). Those reviews by Drs. Trinidad and Dal Pan have since been completed. My views of the postmarketing data were summarized in my February 6th review and Dr. Horn's appended review summarized the in vitro and pharmacokinetic/pharmacodynamic data. Based on these reviews, and the reviews provided by the Controlled Substances Staff and the Office of Surveillance and Epidemiology, we concluded that there were adequate data to support inclusion of the in vitro data and the "drug liking" data (b) (4) in the product labeling.

In regard to the postmarketing data, as I noted in my original review, there were no major inconsistencies between DAAAP and OSE in our interpretation of the findings related to the traditional ("formal") epidemiology studies. There were five investigations that were reasonably well designed and that contained sufficient data for review. These studies included 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) investigation. While some studies suggested a decline in ORF abuse via non-oral routes, other studies did not support such a finding.

We in DAAAP also found that the non-traditional studies provided some support for the sponsor's conclusion that the ORF product's changes to the original formulation's

physiochemical properties are likely to reduce abuse to some degree. These abuse-deterrent features reduce the ability to snort crushed product and reduce drug-liking with administration by snorting. These features also render the product almost impossible to dissolve, syringe, and inject.

While we found that the non-traditional epidemiology studies generally appear to suggest or support a trend of reduced abuse by these routes (i.e., intravenous and intranasal) in the community, we also recognized the limitations of both the non-traditional and the traditional epidemiology studies, (b) (4) The results of the data collectively did, however, support inclusion of the physiochemical property studies and the drug-liking abuse liability studies data in the labeling.

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/s/

BOB A RAPPAPORT
04/16/2013

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Division Director Review

Drug Name: OxyContin Tablets, Reformulated (ORF)
Sponsor: Purdue Pharma
Date of Review: February 6, 2013
Division Director: Bob A. Rappaport, M.D.

The appended review was completed by Dr. Pamela Horn with oversight from Dr. Sharon Hertz, in November of 2012, prior to Dr. Horn's going on extended leave of absence. The review was not filed at that time as Drs. Horn and Hertz were waiting for the epidemiology study reviews to be completed by the Division of Epidemiology in the Office of Surveillance and Epidemiology. Those reviews have since been completed and filed. There are no major inconsistencies between the two divisions in the findings related to the traditional epidemiology studies. However, DAAAP does find that the non-traditional studies provide some support for the sponsor's conclusion that the ORF product's changes to the original formulation's physiochemical properties is likely to reduce abuse to some degree. These abuse-deterrent features are limited to a reduction in the ability to snort crushed product, an almost impossible ability to dissolve, syringe and inject the product for injection and some degree of reduced drug-liking with administration by snorting. While we find that the non-traditional epidemiology studies do appear to, for the most part, support a trend of reduced abuse by these routes in the community, we also recognize the limitations of both the non-traditional and the traditional epidemiology studies submitted in the application, (b) (4) They will, however, support inclusion of the physiochemical property studies and the drug-liking abuse liability studies data in the labeling.

APPENDIX

Medical Officer Review

Drug Name: OxyContin Tablets, Reformulated (ORF)
Sponsor: Purdue Pharma
Date of Review: 11/14/12
Reviewer: Pamela Horn, M.D.
Team Leader: Sharon Hertz, M.D.

Materials Reviewed:
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
    - 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

- Epidemiology studies
    - Division of Epidemiology 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)"* DARRTS, 4/30/12
    - Statistical reviews 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"* DARRTS, Studies 1, 2, and 6: 11/5/12, Studies 3, 4, 5, and 11: 11/9/12
    - Report titled "*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 NDA 7/31/12
- Report on media coverage, submitted to NDA 8/6/12
- Report on information acquired from law enforcement officers, submitted to NDA 8/6/12

Issue

Is there robust and meaningful evidence to conclude that reformulated OxyContin® (ORF) is abuse-deterrent?

Summary of Evidence and Conclusions

The physicochemical differences between ORF and OxyContin appear to make ORF more difficult to use by the intravenous and intranasal routes and, to a lesser extent, to overcome the controlled-release properties by the oral route. The controlled-release properties of ORF can be overcome with chewing and swallowing. The Sponsor concludes that the interim data from epidemiology studies indicates a trend towards less OxyContin abuse since the introduction of ORF. I generally agree that the currently available epidemiological data indicate a decrease in OxyContin abuse. The physicochemical properties of ORF may be responsible for these trends. There is some alignment between the in vitro, pharmacokinetic, and drug-liking data and the epidemiological data, in that the data indicate that the most robust evidence of tamper-resistance is for non-oral routes and abuse by non-oral routes has decreased more than for oral routes.

The consult reviews of the various studies note several limitations and flaws in study design. Additionally, the epidemiologic data represent a small number of data points and much data still remain to be collected. However, these flaws and limitations do not negate the available evidence of a measure of abuse-deterrence. While the amount of data will continue to increase as the ongoing studies are completed, the current evidence is sufficient to draw a conclusion that can be used in making public health decisions.

Despite the significant role OxyContin has played in prescription opioid abuse, because of the availability of other opioids, ORF's abuse-deterrent properties or the introduction of any single opioid product with abuse-deterrent properties alone should not be expected to affect the total incidence or prevalence of opioid abuse or dependence in the U.S.

There is robust evidence that the new formulation of OxyContin has abuse-deterrent features that have translated into a measurable effect on non-oral abuse of OxyContin. This measured effect on OxyContin abuse is meaningful in the context of the current levels of prescription opioid abuse in the U.S.

Background

Purdue Pharma reformulated OxyContin with the goal of making it more difficult to abuse. Although labeling reflecting properties of the new formulation was not requested at the time of the application review, the Sponsor now wants to include language in the OxyContin product labeling describing the abuse-deterrent features of the product. Purdue Pharma submitted a citizen's petition requesting that the Agency require that sponsors who reference ORF (NDA 22,272) demonstrate the abuse-deterrent properties of their formulation in order to receive ANDA marketing approval.

The Agency is in the process of writing a guidance on abuse-deterrent formulations and there is currently no published standard setting the level of evidence required for a formulation to be considered abuse-deterrent.

The Agency approved the NDA for ORF in April 2010. The NDA contained the reports of in vitro studies designed to evaluate the abuse-deterrent physicochemical properties of the formulation. The Controlled Substance Staff reviewed these studies and concluded that the new formulation had abuse-deterrent properties and had demonstrated an advantage over the previous OxyContin formulation by showing that the tablets are considerably more difficult to chew or crush and more difficult to convert to an aqueous solution suitable for intravenous injection.

As a condition of approval, the Agency issued a postmarketing requirement for the Sponsor to conduct epidemiological studies to assess whether the changes made to the OxyContin Tablets formulation result in a decrease in misuse, abuse, addiction, overdose, and death.

The Sponsor submitted an interim report on these studies in December 2011. The Division of Epidemiology reviewed the report in April 2012 and concluded that the interim findings are optimistic regarding an implicit claim of route-specific abuse-deterrence.

Oral and non-oral abuse of OxyContin were significant problems prior to ORF introduction. Data from the ASI-MV® Connect NAVIPPRO™ system indicate that 12% of prescription opioid abusers used OxyContin by the oral route and 18% used OxyContin by non-oral routes from June 2009 to August 2010.[1] However, it appears

[1] ORF Epidemiology Study Program Update July 2012, p. 36

that, historically, the vast majority of the deaths associated with OxyContin were related to oral consumption. DEA medical examiner data from 2002 indicated that 2% of deaths linked to OxyContin were associated with the presence of a recent "injection site" and 0.2% were associated with snorting the drug.[2]

Evidence of Abuse-deterrence: In vitro physicochemical testing

As part of the NDA 22,272 review, the Controlled Substance Staff reviewed seven in vitro studies (named individually under "Materials Reviewed" above) and found that:

- ORF tablets are considerably more difficult to chew or crush compared to the original OxyContin; ORF is less susceptible to immediate release of a high dose of oxycodone.
- ORF can still be crushed to a fine powder using a coffee grinder.
- (b) (4) percent of oxycodone can be extracted from ground ORF using water compared to (b) (4) in the original OxyContin; (b) (4) of oxycodone can be extracted from intact ORF.
- The percentage of oxycodone extracted from ORF using other solvents and different pH levels is less than the original OxyContin.
- It is more difficult to prepare a solution for intravenous injection using ORF than original OxyContin as a result of the inclusion of the excipient polyethylene oxide.
- Obtaining oxycodone free base that could be inhaled from ORF took three times as long as from original OxyContin.

Reviewer Comment: DAAAP found that the results of these studies provided evidence of an incremental improvement in the formulation's resistance to manipulation and approved the new formulation for marketing. In the NDA Summary Review for Regulatory Action, the division noted that the product is not completely resistant to manipulation and that a postmarketing epidemiology study (or studies) would be required to determine the effect of the new formulation on the misuse and abuse of OxyContin.

As a clinical study of the effects of the new formulation on intravenous abuse is not ethically feasible, it is necessary to rely on the in vitro data. The in vitro testing demonstrated a substantial increase in difficulty in attempting to prepare a solution for injection from ORF compared to the original formulation.

The findings from these studies regarding chewing were not supported by the in vivo pharmacokinetic study OTR-1016 (reviewed below), but are otherwise generally in alignment with the findings of studies that were subsequently submitted, reviewed and discussed below.

Evidence of Abuse Potential

[2] http://www.deadiversion.usdoj.gov/drugs_concern/oxycodone/oxycontin7 htm

Purdue completed five studies designed to evaluate the abuse potential of ORF. The Controlled Substance Staff, Clinical Pharmacology, and Statistical teams completed reviews of these studies. The following summary comes from the individual study reports that Purdue submitted to IND 29,038. Overall, these studies indicate that the controlled-release properties of ORF can be overcome when chewed vigorously and swallowed, but the controlled-release properties of ORF were slightly less susceptible to compromise than OxyContin when chewed normally. The ORF formulation scored lower on drug-liking and had a lower Cmax and a longer tmax than OxyContin when taken intranasally, and was less attractive to recreational drug users than OxyContin. ORF created mild irritation and may have less predictable effects than OxyContin when used intranasally.

OTR[3]1016 "A Randomized, Open-Label, Single-Dose, Crossover Study of the Effects of Various Tampering Methods on Exposure to Oxycodone in Fasting Healthy Subjects"

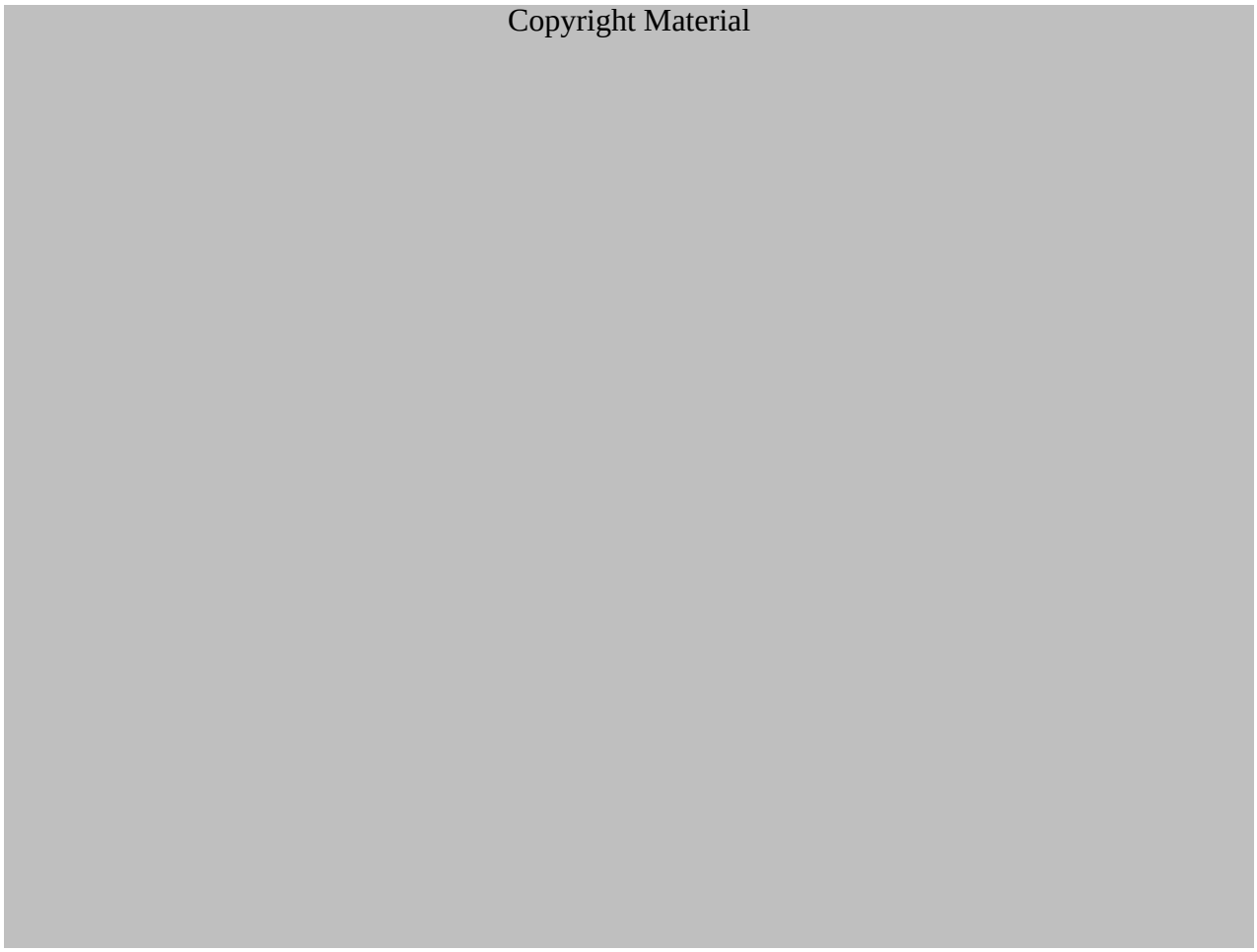
- Objective: Characterize PK profile of chewed and crushed ORF
- Treatments:
  Part A
  - ORF 40 mg swallowed intact
  - ORF 40 mg tablet chewed[4] and swallowed
  - ORF 40 mg tablet particle size reduced by crushing via mortar and pestle, and swallowed
  - ORF 40 mg tablet particle size reduced by crushing via mortar and pestle, chewed, and swallowed
  - ORF 40 mg tablet pre-softened in water, chewed, and swallowed
  - OxyContin 40 mg tablet swallowed intact
  - OxyContin 40 mg tablet chewed and swallowed
  - Reference: immediate-release 40 mg oxycodone solution

  Part B
  - ORF 40 mg vigorously chewed and swallowed
  - OxyContin 40 mg vigorously chewed and swallowed

  Part C
  - ORF 40 mg normally chewed and swallowed
  - OxyContin 40 mg normally chewed and swallowed
- Comparisons
  - Part A: Each ORF and OxyContin condition AUC and Cmax compared to reference
  - Part B: Bioavailability of vigorously chewed ORF and OxyContin 40 mg
  - Part C: Bioavailability of normally chewed ORF and OxyContin 40 mg
- Results
  - vigorous chewing overcame the controlled-release properties of ORF and OxyContin, but swallowing after crushing ORF with a mortar and pestle did not (Part A in figure below)

[3] Purdue referred to reformulated OxyContin as oxycodone tamper resistant tablets or OTR in these studies
[4] chewing in Part A was vigorous chewing (b) (4)

- vigorously chewed ORF and OxyContin had similar overall bioavailability (Part B below)
- normally chewed ORF had lower Cmax and higher tmax than OxyContin (Part C below)



Source: Harris, S. et al., Effects of Various Tampering Methods on Exposure to Oxycodone in Healthy Subjects, 74th Annual Scientific Meeting of the College on Problems of Drug Dependence, Abstract # 242 and Poster # 78 (presented June 12, 2012), Figure 3

- CSS review conclusion
  - 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 ORF 40 mg tablet, a crushed (mortar and pestle) ORF 40 mg tablet, or a pre-softened ORF 40 mg tablet will produce significant levels of drug liking indicative of positive subjective reinforcing effects.
- Clinical Pharmacology review conclusions
  - Part A: Chewing ORF 40 mg or OxyContin (OC) 40 mg results in disruption of the extended-release characteristics of both products with early peak plasma concentrations noted compared to intact ORF or OC treatments.

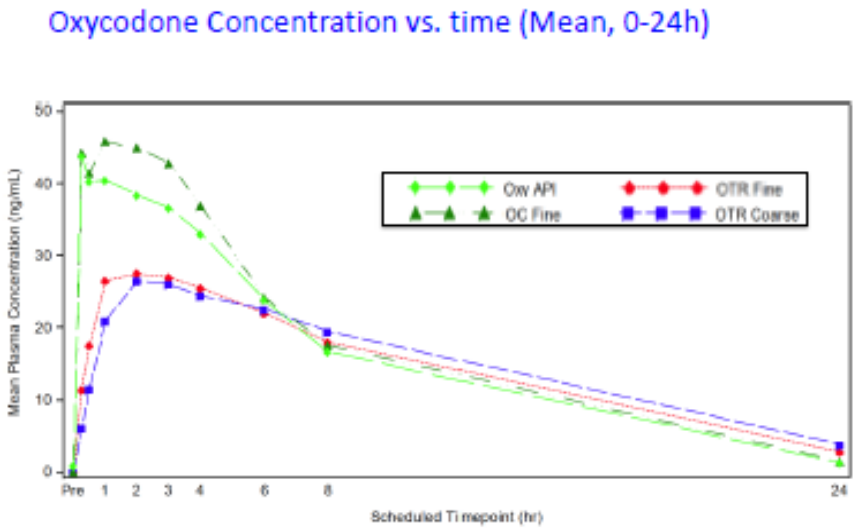
- Part B and C:
    - Upon chewing vigorously, OFR and OC products are bioequivalent with respect to oxycodone Cmax and AUC.
    - Upon chewing normally, ORF formulation resulted in a lower Cmax (76.4%) compared to chewed OC formulation

Reviewer Comment: Swallowed ORF retains some of its controlled-release properties even after it is crushed with a mortar and pestle, less so after it is chewed normally, and not at all if it is chewed vigorously. This represents a minor advantage over OxyContin.

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"

- Objective: evaluate intranasal abuse potential of ORF compared to OxyContin
- Treatments:
    - ORF 30 mg coarsely crushed (ORF_C)[5]
    - ORF 30 mg finely crushed (ORF_F)[6]
    - OxyContin 30 mg finely crushed[7]
    - Oxy API powder
    - placebo finely crushed
- Results
    - ORF_F and ORF_C produced drug liking scores that were lower than crushed OxyContin and Oxy API and higher than placebo
    - Both ORF peak effects were slower (1-2 hrs post-dose) compared to OxyContin and Oxy API (0.5 hrs post dose)
    - Both ORF outcomes were more variable than OxyContin and Oxy API
    - Both ORFs were rated higher on intranasal irritation than OxyContin and Oxy API
    - Mean AUC values were similar across treatment groups and mean Cmax values were higher for OxyContin and Oxy API than for both ORFs
    - ORF PK was more variable than OxyContin and Oxy API and the coarsely crushed ORF was more variable than the finely crushed

[5] cut into (b) (4) using razor blade
[6] prepared using coffee mill
[7] prepared using mortar and pestle



Source: Purdue Pharma Citizen Petition, Exhibit 18, 7/13/12

- Sponsor's conclusions
  - Intranasal ORF has lower abuse potential than OxyContin or Oxy API
- CSS review conclusions
  - There is some evidence that ORF may be less susceptible to intranasal abuse than OC, but on some measures both finely and coarsely crushed ORF scored higher (indicating higher abuse potential) than placebo
- Statistical review conclusions
  - Median responses to ORF were significantly lower than active comparators on analyses of the Drug Liking VAS.
- Clinical Pharmacology review conclusions
  - ORF subjects were more likely to have incomplete insufflation than other treatments
  - ORF had higher variability in PK than the other treatments

Reviewer Comment: The variability in ORF PK and drug liking could make it less desirable to intranasal users. It could also increase the risk of overdose due to lack of predictability in the effect a given dose will have. While the difficulty with insufflation in the ORF groups may make the study results more challenging to interpret, it is indicative of the difficulty associated with using the product intranasally, and is consistent with the CSS conclusion that ORF has lower intranasal abuse potential than OxyContin.

OTR1019 "Relative Attractiveness of Oxycodone TR: Comparative Assessment of Tampering Potential and Recreational Drug User Preferences for Different Opioid Formulations"

- Objective: compare attractiveness for abuse and tampering with ORF, OxyContin and other oxycodone products
- Methods: recreational opioid users were given information cards about ORF, OxyContin and other oxycodone products and were interviewed about the attractiveness of the formulations
- Sponsor's conclusions

- ORF was less attractive than OxyContin and other oxycodone products and more attractive than a hypothetical oxycodone/naltrexone product

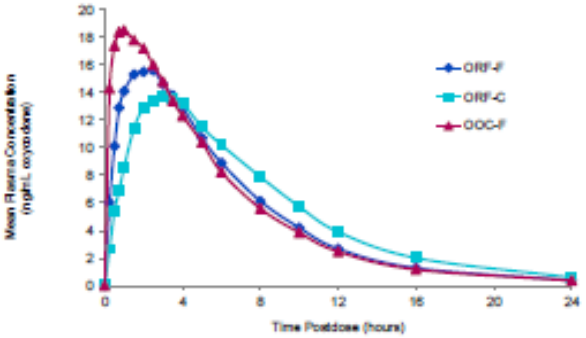
- CSS review conclusions
  - Part 1 of the study, which asked subjects to evaluate attractiveness was poorly designed
  - Part 2 indicates that OFR is less susceptible to physical manipulation than OxyContin using a hammer, pill crusher, mortar and pestle, or X-Acto knife

Reviewer Comment: The study is consistent with the findings of the in vitro studies reviewed as part of original NDA 22272.

OTR1021 "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"

- Objective: compare PK of 10 mg of intranasal finely crushed ORF[8], coarsely crushed ORF[9] and finely crushed OxyContin[10]
- Results
  - 90% CI of AUC was within 80-125% for all comparisons
  - Cmax was lower and tmax was longer for ORF compared to OxyContin (Tmax 1 hr for finely crushed OxyContin, 2 hrs for finely crushed ORF, and 3 hrs for coarsely crushed ORF)

Figure 2. Mean Oxycodone Concentrations Following Intranasal Dosing



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Source: Purdue Pharma Citizen Petition, Exhibit 19, 7/13/12

- CSS review conclusions
  - PK results indicate that ORF may be less susceptible to intranasal abuse
  - The Cmax values compared to those in OTR-1018 indicate that the doses used (10 mg) are unlikely to result in sufficient drug liking
  - The intranasal tolerability study indicates that nasal irritation will not be a deterrent to intranasal abuse
- Clinical Pharmacology conclusions

[8] prepared using coffee mill
[9] cut into (b) (4) using razor blade
[10] prepared using mortar and pestle

- Consistent with the results of OTR-1018, the Cmax of finely crushed and coarsely crushed ORF are lower than finely crushed OxyContin. There are no drug-liking measures to correlate to the PK findings.

Reviewer Comment: The study design, which used lower doses and did not include an evaluation of drug-liking, is less informative than OTR-1018, but the PK results of this study are consistent with the results of OTR-1018. Therefore, the study adds little to the overall conclusions regarding this formulation.

OTR1022 "Single-Center, Randomized, Cross-Over Study in Recreational Opioid Users to Evaluate the Safety of Crushed and Intranasally Administered OTR and OC Placebo Tablets"

- Objective: Assess subjective and administration site tolerability of intranasal ORF and OxyContin
- Results
  - all formulations caused mild congestion and irritation
  - there was residual powder in the nasal cavity with ORF but not OxyContin placebo
- CSS review conclusions
  - The effects of ORF and OxyContin non-active components are not expected to be a deterrent to intranasal abuse

Reviewer Comment: Any observed decrease in intranasal use of ORF would not be expected to be due to irritants in the formulation.

Evidence of Public Health Impact of ORF

Purdue has conducted six epidemiology studies to fulfill the postmarketing requirement and five additional epidemiology studies. The Division of Epidemiology (DEPI) reviewed an interim report on these studies and concluded that the preliminary results were optimistic in demonstrating route-specific abuse-deterrence, but the findings were not mature enough to support an abuse-deterrent claim because there were no formal statistical analyses yet reported and none of the studies had completed the recommended follow-up period of 3-5 years. Purdue submitted an update on these studies on 7/31/12. DEPI is in the process of reviewing it, but the review has not been completed. Purdue concludes that replacing original OxyContin with ORF has resulted in a decrease in misuse and abuse of OxyContin, including a decrease in abuse overall, and abuse by injection, snorting, and smoking, a decrease in diversion, and a decrease in intentional and unintentional poisonings and adverse events. Purdue's findings in the 7/31/12 update are overall slightly less encouraging than those reviewed by DEPI in 4/12, but appear to be generally indicative of a decline in OxyContin abuse, including by non-oral routes, while there was evidence of an increase in abuse of other opioids.

In the update report, Purdue numbered the studies and summarized the data sources and endpoints addressed in the studies (reproduced below).

Table 1. Summary of endpoints measured by Epidemiologic Studies of ORF: Post-marketing requirements

#	Studies	Abuse				Patients	Accidental Exposures
		Rates of Abuse	Diversion	Routes of Abuse	Poison center abuse exposures		
1	NAVIPRO – Substance Abuse Treatment Centers	✓		✓			
2	Kaiser Permanente – Overdoses among insured members					✓	✓
3	RADARS – Poison Centers				✓	✓	✓
4	National Surveys – RADARS College Survey, NSDUH	✓		✓			
5	RADARS – Drug Diversion Program		✓				
6	Prescription Monitoring Programs – doctor-shopping patients		✓				

Source: ORF Epidemiology Study Program Update July 2012, p. 7

Table 2. Summary of endpoints measured by Epidemiologic Studies of reformulated OxyContin: Supplemental studies

#	Studies	Abuse				Patients	Accidental Exposures
		Rates of Abuse	Diversion	Routes of Abuse	Poison center abuse exposures		
7	Internet monitoring for recipes of abuse	✓		✓			
8	Abuser cohort in Kentucky	✓		✓			
9	IMS - prescriptions nationally and in ADD Program		✓				
10	Purdue Adverse Event database	✓				✓	✓
11	National poison data system – Poison Centers	✓			✓	✓	✓

Source: ORF Epidemiology Study Program Update July 2012, p. 7

Division of Epidemiology review

In the April 2012 review, DEPI considered studies 1, 2, 3, and 11 (see tables 1 and 2 above for data source and endpoints) to be pivotal to understanding ORF's effect on OxyContin abuse and the other seven studies to provide additional context to the societal,

behavioral, and clinical aspects of OxyContin abuse. Below are the key findings from the DEPI review.

- Overall OxyContin abuse and desirability
  - In study 1, prevalence of past-month abuse per all individuals entering substance abuse treatment decreased by (b) (4) after the introduction of ORF. Similarly, in study 11, intentional-abuse exposures per quarter-years as reported to poison control centers decreased by (b) (4).
  - In study 5, both drug diversion cases and average street price of OxyContin decreased after the introduction of ORF.
  - Studies 3 and 7 had mixed results,
- OxyContin compared to other opioids
  - Studies 2, 5, and 8 found a decrease in OxyContin abuse or drug diversion and an increase in abuse or diversion of IR oxycodone.
  - Studies 1 and 8 found a reduction in OxyContin abuse and an increase in oxymorphone abuse.
- OxyContin abuse by routes of administration
  - Study 1 found a (b) (4) decrease in the prevalence of oral routes of OxyContin abuse and a 70% decrease in non-oral routes of abuse among all individuals entering substance abuse treatment.
  - Study 3 found a decline in injection and inhalation routes following introduction of ORF, but the number of non-oral exposures was small.

Purdue's July 2012 update

Study 1: Routes and Rates of OxyContin Abuse Among Patients in Substance Abuse Treatment Programs in the ASI-MV® Connect NAVIPPRO™ System

Objective: Characterize routes of administration patterns and abuse associated with ORF.
Data Source: NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV Connect)
Design: A prospective observational surveillance study
Methods: Data collected from a sample of substance abuse treatment centers in the United States using the NAVIPPRO Addiction Severity Index- Multimedia Version (ASI-MV) Connect system.
Population: Male and female adult substance abuse patients at substance abuse treatment centers.
Outcomes: Past 30-day abuse and past 30-day abuse via specific routes of administration
Duration of Baseline Data: 14 months prior to August 2010
Study Period: Prospectively from August 2010 to December 2012
Final Report Date: June 5, 2013
Sponsor's Key Findings to Date (through March 2012)

- Data updated through 1Q2012
- The percent of individuals abusing original versus reformulated OxyContin per 100 individuals assessed in substance treatment declined (b) (4) overall, (b) (4) through oral routes and (b) (4) through non-oral routes following ORF introduction.

- In OxyContin abusers, injecting decreased from (b) (4) snorting decreased from (b) (4) and smoking decreased from (b) (4)
- The number of individuals abusing OxyContin per 100 individuals abusing any prescription opioid in substance treatment declined (b) (4) overall, (b) (4) through oral routes and (b) (4) through non-oral routes following ORF introduction.
- There was a (b) (4) increase in abuse of ER oxymorphone and a (b) (4) increase for ER morphine.
- There was a slight increase in non-oral routes of abuse for ER Oxymorphone during the same period (snorting increased from (b) (4) smoking increased from (b) (4) and injecting increased from (b) (4)

The following figure is from Purdue's July 2012 report p.39

Figure 11. Percent of abuse via specific ROA* for OxyContin before and after introduction of ORF†

Statistical review conclusion: The data for 20 months post ORF supports the hypothesis of lower rates of abuse with ORF, but the findings beyond the second quarter of data are very similar with OC and ORF.

Reviewer Comment: This interim report included the majority of the data (1.5 yrs out of 2.25 yrs) for this study. The decrease in oral and non-oral OxyContin abuse is less than in the last interim report (b) (4) respectively compared to (b) (4)

and 70% in April 2012 Depi review). If this trend continues, the changes in abuse will be largest right after introduction of the new formulation. There was a decrease in abuse by all non-oral routes of administration. This decrease is consistent with the findings in the in vitro and abuse liability studies that predicted ORF would be more difficult to abuse by non-oral routes.

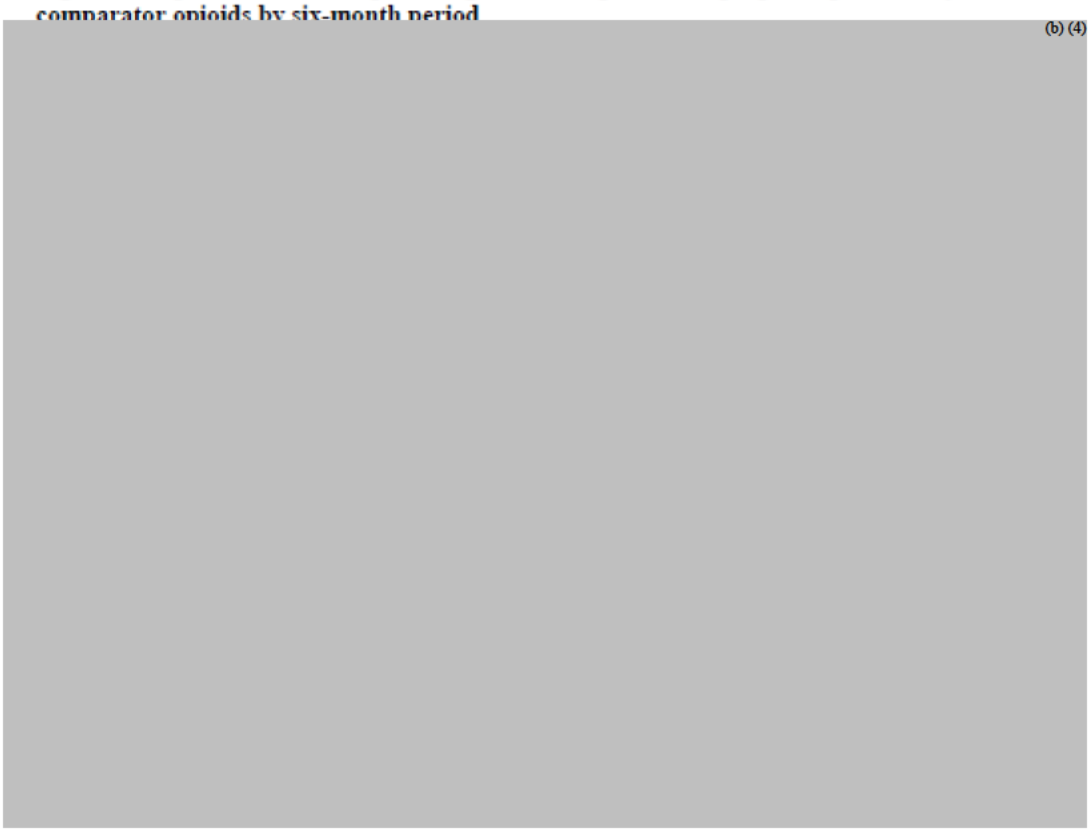
Study 2: Changes in Rates of Opioid Overdose and Poisoning Events in the Kaiser Permanente Health System with the Introduction of Reformulated OxyContin

Objective: To estimate and compare rates of opioid overdose and poisoning (OOP) events before and after the introduction of ORF among individuals dispensed OxyContin, as well as for individuals dispensed three groups of comparator opioids: a) other ER opioids, b) IR, SE oxycodone, and c) all other prescription opioids.
Data Source: Kaiser Permanente electronic medical records (EMR) databases.
Design: Longitudinal study using EMR databases
Methods: Chart audits conducted for 102 opioid overdose and poisoning events identified through ICD-9 and ICD-10 codes. Cases systematically selected to obtain a sample that included the full range of individual characteristics (age, gender), diagnoses, and involved drugs/medications to allow assessment of electronic medical record accuracy across a wide range of events and patients.
Population: Members of the Kaiser Permanente Northwest and Northern California regional health care system
Outcomes: Opioid overdose and poisoning events identified from ICD codes in the Kaiser EMR
Duration of Baseline Data: One year for estimating change in rates of OOP events; 7 years for estimating change in trends of OOP events prior to August 2010
Study Period: Prospectively from August 2010 to December 2012
Final Report Date: June 5, 2014
Sponsor's Key Findings to Date

- Preliminary analyses up to July 2011 do not show a decline in opioid overdose and poisoning events associated with an active prescription of OxyContin.
- Most cases of OOP identified were by oral route of administration (b) (4)), with drug obtained through the patient's own prescription, and there was evidence of misuse identified in the chart audit.
- There were precipitous declines in the number of prescriptions of OxyContin and generic ER oxycodone at Kaiser Permanente that began in the pre-ORF period

The following figure is from Purdue's July 2012 report p.66

Figure 16. Opioid overdose or poisoning event rate per 10,000 people dispensed OxyContin and comparator opioids by six-month period



Statistical Review Conclusion: There is not enough information to comment on the study results at this time.

Reviewer Comment: This study has preliminary analyses for slightly less than half the reporting period. Thus far, there is no evidence of a decline in overdose or poisonings. Of note, the vast majority of overdoses and poisonings identified were by the oral route. If one were to draw conclusions from this study about the general population, one might conclude that the results indicate that ORF, which had the most convincing data in non-epidemiology studies for being abuse-deterrent by non-oral routes, will be unlikely to have an impact on overdoses and poisonings. However, we are unable to draw a well-founded conclusion based on the limited data available at this time.

Study 3: Exposures Reported to Poison Centers in the RADARS System
Objectives:

- To estimate the change in the rate of intentional and unintentional exposure cases for OxyContin and comparator opioids before and after the introduction of ORF.
- To assess changes in case fatality rates for OxyContin and comparator opioids before and after the introduction of ORF.
- To compare the mortality rate for OxyContin for the period before and after the introduction of ORF to that for comparator opioids.

Data Source: RADARS System Poison Center Program
Design: Observational interrupted time series
Methods: All human exposure cases reported to Poison Centers participating in the RADARS System were analyzed. The outcome variables are exposures counts (intentional and unintentional), mortality rates, and case fatality rates for OxyContin and comparator opioids.
Population: General population
Outcomes:

- Intentional exposures of OxyContin and comparator opioids
- Fatalities with OxyContin and comparator opioids
- Unintentional exposures of OxyContin and comparator opioids
- Total exposures of OxyContin and other opioids

Duration of Baseline Data: 7 years prior to August 2010
Study Period: Prospectively from August 2010 to December 2012
Final Report Date: June 5, 2013
Sponsor's Key Findings to Date

- OxyContin intentional abuse exposure and therapeutic error rates based on population and unique recipients of drug dispensed (URDD) declined in Q3 and Q4 2011 and Q1 2012
- The URDD intentional abuse exposure rate for other prescription opioids also declined in the period after ORF introduction, but the rate for OxyContin declined more

The following figure is from Purdue's July 2012 report p.86.

Figure 27. Percent change in URDD-adjusted rates of RADARS System Poison Center exposures in period following introduction of ORF relative to baseline rates in the year prior to ORF introduction (3Q2009 to 2Q2010)

Statistical review conclusions

- The outcome measures defined in the protocol are not consistent with the ones reported in the results section:
  - The intentional abuse outcome reported in the results section is a subset of the intentional exposures outcome in the synopsis.
  - The therapeutic errors outcome reported in the results section is a subset of unintentional exposures outcome in the synopsis.
- The Sponsor provided insufficient information about the models and corresponding hypothesis tests to allow comment on the analysis result.

Reviewer Comment: These findings indicate a decrease in intentional abuse exposures and therapeutic errors for OxyContin after introduction of ORF that were not observed for other opioids during the same period or were larger for OxyContin than for other opioids. However, Figure 27 above demonstrates that intentional exposures and unintentional general exposures (age 12 or younger) have declined for OxyContin as well as oxycodone IR and other prescription opioids and, in these analyses, it appears that OxyContin did not have a larger decrease than oxycodone IR and other prescription opioids. Therefore, the results available indicate that adverse events associated with misuse and abuse of OxyContin have decreased overall, but OxyContin did not distinguish itself from other opioids. The introduction of ORF may have contributed to these results.

Study 4: Using Surveys to Assess the Impact of Reformulated OxyContin
Objective: To estimate trends in the prevalence of abuse of OxyContin and other pharmaceutical opioids for the period before and after the introduction of ORF
Data Sources:

1. National Survey on Drug Use and Health (NSDUH)
2. Monitoring the Future survey (MTF)
3. RADARS System College Survey (RADARS-CS)

Design: Repeated cross-sectional surveys
Methods:
NSDUH- A survey of the US household population age 12+ using computer-assisted interview conducted annually with approximately 60,000 respondents at each assessment.
MTF- A school-based survey of students in 8th, 10th, and 12th grades conducted annually with approximately 50,000 respondents at each assessment.
RADARS System College Survey- Online, self-administered national survey of college students conducted three times per year on a sample of approximately 2000 respondents per assessment.
Population: General population
Outcomes: Past year non-medical use of OxyContin and other opioids, frequency of use, recent onset, persistence, DSM-IV dependence
Duration of Baseline Data: 6 years prior to August 2010
Study Period: Prospectively from August 2010 to December 2012
Final Report Date: June 5, 2014
Sponsor's Key Findings to Date

- Data covering post-ORF period were not available from NSDUH.
- Prevalence of OxyContin non-medical use in past 3 months in the RADARS College survey was unchanged in pre- versus post-ORF periods ((b) (4) versus (b) (4), respectively).
- Data from the 2011 MTF study indicate no significant change in prevalence of OxyContin relative to earlier years.
- The high prevalence rates in the MTF compared to the rates for the similarly aged respondents in the NSDUH raise concerns about the validity of comparing results across the two surveys. The Sponsor concluded that the NSDUH is likely to be a better estimate because the NSDUH survey has more lead-in and clarity in the questions asked and the MTF may reflect more confusion between brand and generic products.

Statistical review conclusions:

- The reviewer cannot evaluate the analysis results, because there was an inadequate description of the statistical method in the report.
- NSDUH is a reliable data source
- The reviewer agrees with the Sponsor that the discrepancy in prevalence rates between NSDUH and MTF raises concern for the validity of MTF.

Reviewer Comment: In the available data, there was no change in non-medical use of OxyContin detected. These results do not support the hypothesis that ORF n has had a public health impact. However, the NSDUH data were not available and one of the other surveys, MTF, may not be reliable. Therefore, these study results should be considered in this context and contribute less to the weight of evidence than other studies, such as Study 1.

Study 5: Law Enforcement Events in the Drug Diversion Program of the RADARS System

Objectives:

- To compare the rate of drug diversion cases for OxyContin and comparator opioids before and after the introduction of ORF
- To compare average street prices for OxyContin and comparator opioids before and after the introduction of ORF

Data Source: RADARS System Drug Diversion Program

Design: Observational interrupted time series

Methods: Quarterly questionnaires eliciting information on the number of new cases of diversion and street price of specific diverted products in the United States investigated by law enforcement and regulatory agencies.

- Reported diversion cases in the United States per quarter and drug group
- Reported street price per quarter

Population: General population

Outcomes:

- Counts of drug diversion cases reported to the RADARS System Drug Diversion Program
- Street prices reported to the RADARS System Drug Diversion Program

Duration of Baseline Data: 8 years prior to August 2010
Study Period: Prospectively from August 2010 to December 2012
Final Report Date: June 5, 2013
Sponsor's Key Findings to Date

- Relative to pre-ORF rates, OxyContin population-adjusted diversion rates declined by (b) (4) in 3Q2011, (b) (4) in 4Q2011, and (b) (4) in 1Q2012.
- Rates for IR oxycodone remained higher than those in the pre-ORF period.
- Street price of ORF was (b) (4) lower than that for original OxyContin in the post-ORF period through 1Q2012.

The following figure is from Purdue's July 2012 report p.99

Figure 33. Percent change in population-adjusted rate of drug diversion for OxyContin and other opioids in the post-ORF period relative to the average rate in the year prior to ORF introduction (3Q2009 to 2Q2010)

Statistical review conclusion: The Sponsor provided insufficient information about the models and corresponding hypothesis tests to allow comment on the analysis result.

Reviewer Comment: These results appear to indicate that there is less diversion of OxyContin since ORF introduction and the ORF formulation is less valued for illegal sale.

Study 6: Doctor-shopping for OxyContin as Measured by Prescription Monitoring Programs
Objectives: To compare the rate of doctor-shopping for OxyContin and comparator opioids before and after introduction of ORF
Data Source: Data collected by Prescription Monitoring Programs (PMP)
Design: Doctor-shopping is defined as visiting more prescribers and pharmacies than necessary to obtain prescriptions for legitimate medical reasons so that the excess opioid

supply can be abused or sold for abuse. This study is an open cohort study comparing changes in doctor-shopping for OxyContin and comparator opioids over time in state PMPs

Methods: Among all individuals prescribed a controlled substance in a specified state, changes in the number of individuals who meet the operational definition of doctor-shopping per census population of the catchment population or per total individuals prescribed an opioid in the PMP per 6-month or one-year period will be evaluated before and after the introduction of the new formulation.

Population: The study catchment population consists of all residents of the states whose prescriptions are reported to the PMPs that participate in this study.

Outcomes: Number and rates of individuals who doctor shop for OxyContin and comparator opioids

Duration of Baseline Data: 2-3 years prior to August 2010

Study Period: August 2010 to December 2012

Final Report Date: June 5, 2013

Sponsor's Key Findings to Date

- State PMPs: The Sponsor reported the results from Ohio only and stated that the preliminary analysis of Ohio PMP data using various combinations of multiple prescribers and pharmacies demonstrated a decline in doctor shopping as defined by 4 or more prescribers and 4 or more pharmacies.

- IMS LRx
    - Analysis of doctor-shopping using IMS LRx patient longitudinal data demonstrated a decline in rates of doctor shopping following introduction of ORF based on counts of prescribers and pharmacies in which OxyContin prescriptions overlapped.
    - Based on a definition of more than 2 prescribers and more than 3 pharmacies, doctor shopping rates declined from (b) (4) in Jan-Jun 2010 to (b) (4) in Jul to Dec in 2011.
    - Extending this definition to include at least one prescription for OxyContin to be paid for by cash led to a larger relative decline from (b) (4) in the pre- vs. post-ORF periods.

Statistical review conclusions:

- PMP analysis of Connecticut, Ohio, and Massachusetts PMPs show no difference in counts and rates of doctor shopping after ORF introduction.
- The IMS LRx results are misleading because the cut-off criteria for number of prescribers and pharmacies lack standard support and there are too few data points.

Reviewer Comment: In both the state PMPs and the IMS LRx, there was a very small proportion of cases of doctor shopping identified. The results of the PMP analysis indicate that there was no difference before and after introduction of ORF, but the IMS LRx analysis indicates that there was a reduction. It is unclear if this analysis can be relied upon based on the conclusions by the statistical reviewer.

Study 7: Monitoring Internet Chat Room Discussions about OxyContin Abuse
Objectives:

- Characterize degree of online discussions about ORF and comparator drugs
- Characterize nature of online discussions about ORF and comparator drugs
- Assess longitudinal trends in degree and nature of online discussions, particularly pre/post ORF.

Data Source: Web Informed Services (WIS) proprietary data source for NAVIPPRO.
Design: Qualitative research.
Methods: Analysis of posts in internet chat rooms where prescription opioid abuse and tampering methods are discussed.
Population: Drug users who frequent websites with active discussion devoted to prescription medication abuse.
Outcomes:

- Degree (amount of discussion, size of the population participating in discussion) of online discussions about ORF and comparator drugs.
- Nature (routes of administration, extraction techniques, sources of procurement, negative consequences; endorsing, discouraging, mixed, unclear) of online discussions about ORF and comparator drugs.

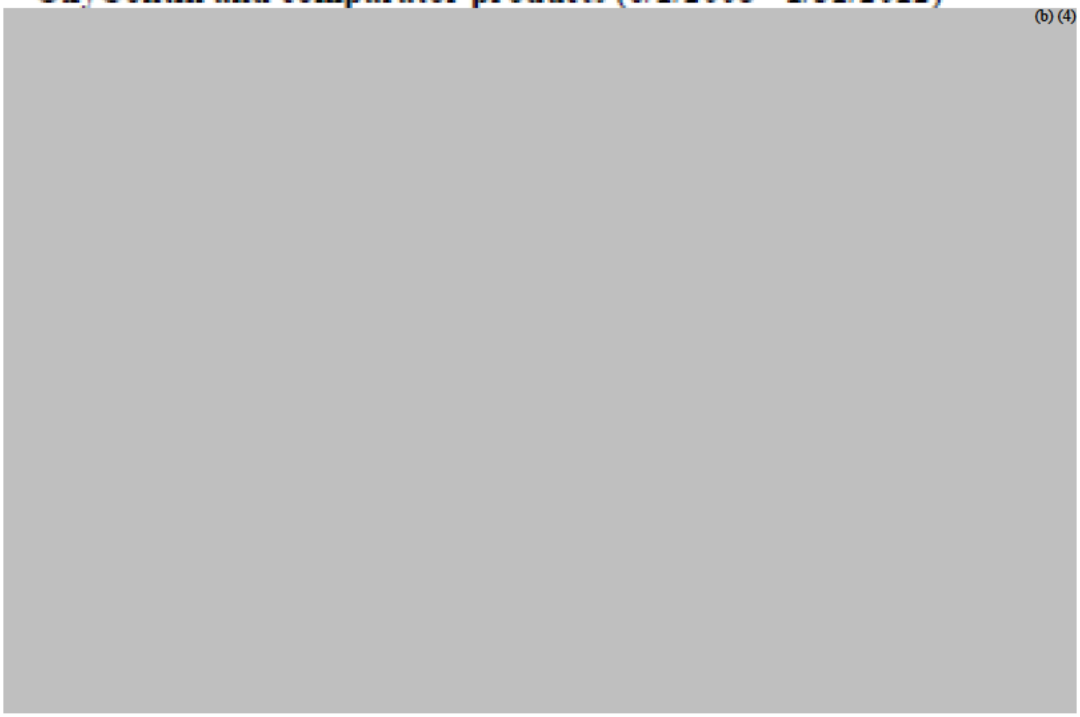
Duration of Baseline Data: 2 years prior to August 2010
Study Period: Prospectively from August 2010 to April 2012
Final Report Date: June 5, 2013
Sponsor's Key Findings to Date

- People determined to tamper with ORF claimed they were able to abuse ORF via methods that require tampering, but overall frequency was low.
- Out of (b) (4) posts between the introduction of ORF and April 2012, there were (b) (4) posts (b) (4) that reported injecting ORF and (b) (4) posts (b) (4)) that reported snorting.
- The proportion of posts that were labeled as encouraging were lower for OxyContin than for Vicodin or Dilaudid and the discouraging and unclear posts were higher since ORF introduction.
- The proportion of authors mentioning OxyContin products is still higher for OxyContin than Vicodin or Dilaudid as of the end of 2011, all of them have decreased, but OxyContin has decreased the most (see figure below).

The figure below is from Purdue's July 2012 report, p.124

Figure 36. Proportion (P) of authors (per 100) mentioning OxyContin and comparator products (6/1/2008 - 1/31/2012)

(b) (4)



Reviewer Comment: This study indicates a decreased interest in OxyContin overall, which is supportive of a positive public health impact. The discussions on manipulation for injection and intranasal use represented a small proportion of the activity on the websites, involved complicated and labor intensive methods such as (b) (4) **and are encouraging overall towards the abuse-deterrent properties of ORF.**

Study 8: Changes in Abuse Patterns in a Cohort of People Abusing OxyContin in Rural Kentucky

Objectives: Determine substance use history for 200 self-reported OxyContin abusers recruited by the respondent-driven sampling method:

- Identify methods of preparation and routes of administration for pharmaceutical and illicit opioids
- Identify changes in drug use patterns after the introduction of ORF.
- Qualitative interviews among a subset of participants to further understand the impact of the reformulation on drug use patterns.

Data Source: Interviewer-administered questionnaires; qualitative interviews.

Design:

- Longitudinal, prospective surveys of current opioid abusers (n=200).
- Qualitative face-to-face interviews of a subset of participants (n=25).

Population: Abusers residing in Perry County, Kentucky.

Methods:

- Structured, interviewer-administered questionnaire to collect quantitative data on demographics and use of the following substances to get high: alcohol, heroin, methadone, OxyContin, other oxycodone, hydrocodone, hydromorphone, fentanyl, benzodiazepines, cocaine, crack cocaine, methamphetamine, and marijuana.
- Face-to-face qualitative interviews examining changes in drug use patterns, changes in individual drug use patterns, sources of prescription drugs, and past and current illicit and prescription drug use.

Outcomes

- Routes of abuse of OxyContin with original and ORF
- Methods of "tampering" with OxyContin to prepare it for abuse with original and ORF

Duration of Baseline Data: Retrospective questionnaire at the time of the introduction of ORF

Study Period: Prospectively from December 2010 to September 2011

Final Report Date: September 2012

Sponsor's Key Findings to Date

Demographics

- Over (b) (4) of subjects had injected drugs (b) (4) of these had injected prescription opioids).
- Lifetime substance use was (b) (4) for hydrocodone, benzodiazepines, illicit methadone, cocaine, alcohol, and marijuana in addition to oxycodone.

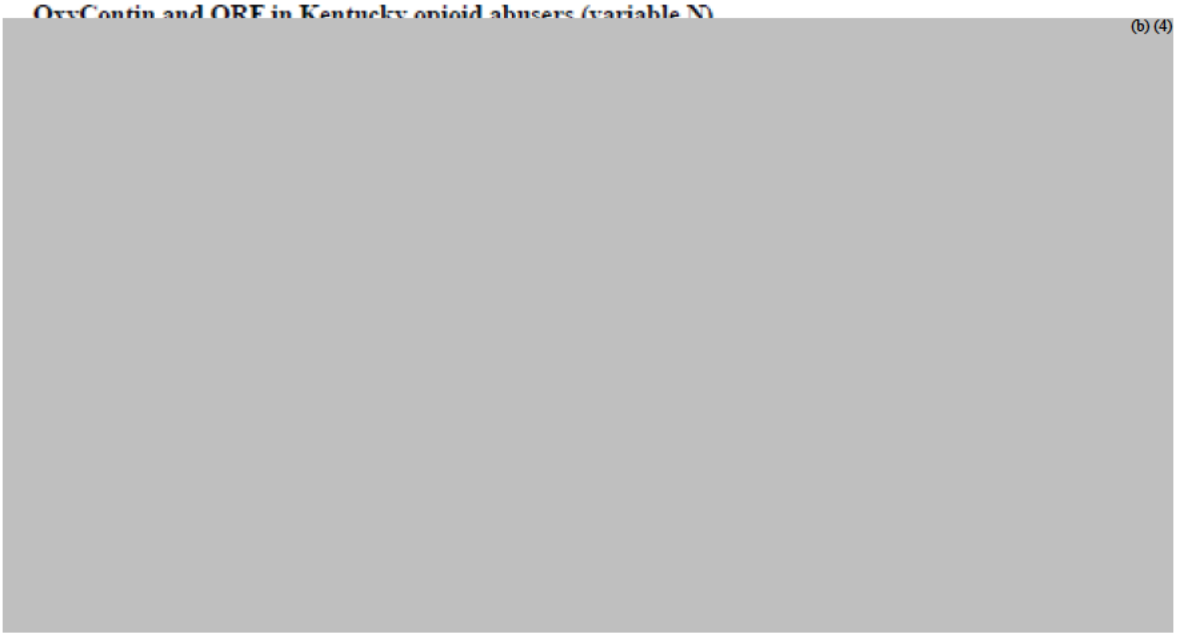
Quantitative surveys

- Pre-ORF original OxyContin abuse was much lower by oral routes than by injection and snorting.
- In post-ORF assessment, (b) (4) reported abuse of original OxyContin and (b) (4) report abuse of other oxycodone compared to (b) (4) for ORF.
- Non-oral ORF abuse was less frequent than that for other oxycodone.
- On average, ORF was injected (b) (4) days in past 30 days versus (b) (4) days for other oxycodone.
- On average, ORF was snorted (b) (4) days in past 30 days versus (b) (4) days for other oxycodone.

The figure below is from Purdue's July 2012 report, p. 139

Figure 41. Changes in frequency of abuse (days/month) by route of administration for original OxyContin and ORF in Kentucky opioid abusers (variable N)

(b) (4)



Qualitative interviews

- In this population, the reformulation decreased ORF desirability and deterred ORF abuse, particularly via non-oral routes. However, the reformulation did not deter abuse of other opioids, as other oxycodone replaced OxyContin as the most popular, most available, and most misused drug.

Reviewer Comment: Weaknesses of the study include retrospective reporting of the pre-ORF period and a sample from a single area of the country. However, for this population, it appears that ORF has had an impact on OxyContin abuse by non-oral routes in particular. Unfortunately, subjects in the study abuse a variety of opioid and non-opioid substances, were able to switch to other opioids like oxycodone IR, and the study did not indicate that these subjects have benefitted from the new formulation in terms of addiction or its psychosocial consequences.

Study 9: Changes in OxyContin Prescriptions as an Indicator of Diversion

Objectives:

- To assess changes in opioid prescribing before and after the introduction of ORF for three groups of prescribers
  - All prescribers in the United States
  - High risk Prescribers identified through the Abuse and Diversion Detection (ADD) program
  - Comparator prescribers
- To estimate the magnitude of change in prescribing for higher versus lower strengths of OxyContin
- To estimate trends in prescribing of other opioids (e.g., other long-acting opioids or IR SE oxycodone)

- To estimate the extent of reductions in OxyContin prescribing that are accounted for by ADD prescribers
- To estimate changes in number of OxyContin prescriptions that are paid for by cash

Data Source: IMS Xponent data
Design: Multiple cross-sectional measures of monthly prescriptions
Methods: Analysis of prescribing patterns for all prescribers, high-risk prescribers, and comparator prescribers utilizing IMS Xponent data
Population: Prescribers in United States
Outcomes: Changes in numbers of prescription for OxyContin and other opioids
Duration of Baseline Data: August 2009 to July 2010
Study Period: August 2009 to July 2011
Final Report Date: Study Completed
Sponsor's Key Findings to Date

- Overall, there was a small decline in number of OxyContin prescriptions post- versus pre-ORF (b) (4).
- Decline specific to higher dosage strengths
  - (b) (4) decline in 80 mg strength
  - (b) (4) decline in 40mg strength
  - Increase or no change for lower dosage strengths
- Declines specific to cash payment
  - (b) (4) decline in OxyContin prescriptions with cash payment
  - Relatively small declines in other payment types (b) (4)
- Large declines in numbers of OxyContin prescription for physicians identified through ADD program relative to comparator prescribers
  - (b) (4) decline among ADD prescribers
  - (b) (4) ADD prescribers account for (b) (4) of decline in 80mg OxyContin prescriptions nationwide following introduction of ORF
- Concurrent increase in prescriptions of original OxyContin in Windsor, Ontario across the United States border from Detroit.

Epidemiology review conclusion (4/12): The findings for ADD prescribers could be a result of an unstable number of ADD prescribers (for example, due to arrests or license suspensions). The reviewer points out that the introduction of ORF occurred the same quarter as a spike in drug diversion cases and may have affected ADD prescribing habits.

Reviewer comment: The epidemiology conclusion was included here because the study is complete. Therefore, the epidemiology review conclusion from the 4/12 review is based on all the same data as are contained in the Sponsor's July 2012 report.

The switch to ORF is related temporally to prescribing patterns that are thought to be less risky, such as prescription of lower strengths, fewer cash payments, and decreased prescribing by high-risk prescribers. There could be a causal relationship with ORF introduction or these changes could be due to other external factors, such as changes in law enforcement efforts. The results are compatible with

the hypothesis that ORF has abuse-deterrent properties capable of impacting public health.

Study 10: Analyses from the Adverse Event Database on Overdose Mortality, Drug Abuse AEs, and Patient Medication Errors
Objectives: Review and analyze OxyContin post-marketing cases associated with drug abuse, intentional drug misuse, medication errors/ maladministration and overdose involving original OxyContin versus ORF.
Data Source: Purdue's International Drug Safety Database (ARGUS)
Design: Query-based database search
Methods: Review and analysis of post-marketing cases utilizing Purdue's drug safety database (ARGUS)
Population: Post-marketing cases contained in Purdue's drug safety database
Outcomes: Number of original OxyContin versus ORF post-marketing cases of drug abuse, intentional drug misuse, medication errors/ maladministration and overdose
Duration of Baseline Data: January 1, 2010 to December 31, 2010
Study Period: January 1, 2011 to December 31, 2011
Final Report Date: Ongoing
Sponsor's Key Findings to Date

- The number of unique cases with a Drug Abuse preferred term for ORF in 2011 was 44% lower than for OC in 2010 (499 vs. 894 patients), and fatal cases were 71% lower for ORF in 2011 (n=14) compared to OC in 2010 (n=48).
- The number of unique cases with an Overdose preferred term was 50% lower for ORF in 2010 (n=120) compared to OC in 2011(n=240), and fatal cases were 51% lower (n=79 vs. 162).
- The number of unique cases with a Medication Error/ Maladministration PT declined by 16% for ORF in 2011 (n=131) compared to OC in 2010 (n=155), and fatal cases were 50% lower (4 vs. 8).
- No large changes to Purdue's adverse event reporting system occurred during this period of observation.

Reviewer Comment: The comparisons between ORF in 2011 and OC in 2010 reported exclude the first 4 months of ORF shipment (August 2010 through December 2010). During these months, there was a spike in adverse event reports in all categories mentioned above. However, because the spike is expected with the entry of a new formulation to the market, the choice to compare ORF data starting in 2011 may be appropriate. The changes noted in this study may be a result of known factors that affect reporting as well as unknown factors and the evidence quality is weak compared to the better-designed studies.

Study 11: Changes in Poison Center Exposure Rates for OxyContin, other SE oxycodone and heroin in the National Poison Data System.
Objectives: To assess changes in Poison Center Exposure Rates for OxyContin, other SE oxycodone and heroin in the National Poison Data System with the introduction of ORF
Data source: American Association of Poison Control Centers' National Poison Data System

Design: Longitudinal observational study of exposures to drugs of interest in all poison centers in the United States between January 1, 2007 and December 31, 2011
Population: All poison centers that cover the United States population
Methods: Measurement of the number of exposures to OxyContin, heroin, and SE oxycodone per quarter reported to a national network of all poison centers in the United States
Outcomes: Exposures to OxyContin, heroin, and SE oxycodone (excluding OxyContin) based on calls to poison centers by individual callers or reported to poison centers by emergency departments. Intentional exposures are defined as a purposeful action that results in an exposure. Unintentional exposures are defined as an exposure that results from an unforeseen or unplanned event.
Duration of baseline data: The period between 3Q2009 through 2Q 2010 was the "before" ORF period
Study period: The time between 4Q2010 through 4Q2011 was the "after" ORF period
Sponsor's Key Findings to Date (unadjusted for population or number of prescriptions)

- OxyContin exposures declined post- versus pre-ORF:
  - (b) (4) for all exposures (from (b) (4) per quarter)
  - 19% for intentional exposures (b) (4) per quarter)
  - 30% in intentional abuse exposures (b) (4) per quarter)
  - (b) (4) for unintentional exposures (b) (4) per quarter)
  - (b) (4) for therapeutic errors among patients (b) (4) per quarter)
- Intentional single-entity oxycodone exposures increased (b) (4) ((b) (4) per quarter)
- Intentional heroin exposures increased (b) (4) ((b) (4) per quarter) (cannot be adjusted by prescriptions)

The following figures are from Purdue's July 2012 report, p.185-188, and summarize the effects of adjusting for population and number of prescriptions:

Figure 65. The Effect of Adjusting for Number of Prescriptions and Population Covered on Intentional Abuse Exposures

A. OxyContin

Source: Exposures from NPDS, Prescriptions from SDI VONA. Baseline period: 3Q2009 to 2Q2010

B. Other oxycodone products excluding OxyContin

Source: Exposures from NPDS, Prescriptions from SDI VONA. Baseline period: 3Q2009 to 2Q2010

Figure 66. The Effect of Adjusting for Number of Prescriptions and Population Covered on Unintentional Therapeutic Errors

A. OxyContin

Source: Exposures from NPDS, Prescriptions from SDI VONA. Baseline period: 3Q2009 to 2Q2010

B. Other oxycodone products excluding OxyContin

Source: Exposures from NPDS, Prescriptions from SDI VONA. Baseline period: 3Q2009 to 2Q2010

Statistical review conclusions:

- As shown in figure 65A, after adjusting for the number of prescriptions, OxyContin intentional exposures declined by a much smaller magnitude during the post-ORF period.

- As shown in figure 65B, the increase in intentional exposures in other oxycodone products is lost when one adjusts for prescriptions.
- As shown in figure 66, therapeutic errors were generally the same after adjusting for the number of prescriptions.
- The prescription adjusted rates may be more interpretable for assessing the effect of ORF than the population adjusted rates.
- No formal statistical testing was conducted.

Reviewer Comment: After adjustment for number of prescriptions, there is still evidence of a decrease in intentional OxyContin exposures without a corresponding decrease in other oxycodone products. The decreases in OxyContin intentional exposures are aligned with Study 3, but the lack of decrease in other oxycodone products in this study differentiates OxyContin from other oxycodone products and could be evidence of an effect of ORF. Overall, these findings could be supportive of a public health impact of ORF.

Evidence of ORF's impact in law enforcement and news reports

On 8/6/12, Purdue submitted reports on law enforcement information and news articles concerning OxyContin to NDA 22272 at DAAAP's request.

Law Enforcement Officer Information

The report contained a listing of statements made by Purdue's Law Enforcement Liaison and Education trainers from 2010-2012 regarding their interactions with law enforcement officers during training program sessions. Generally, the trainers report that the officers had seen a decrease in the demand and street price of OxyContin. Some reported that people were using (b) (4) to manipulate the new formulation and others reported that people couldn't manipulate the new formulation and did not have an interest in trying to sell or obtain it.

OxyContin News Article Summaries

The report consisted of a list of excerpts from news articles from 2010-2012 that mention reformulated OxyContin by searching a news monitoring service by keyword "OxyContin." Articles generally credit the difficulty in using the new formulation intranasally and intravenously with the observed decrease in OxyContin abuse and note the shift in popularity from OxyContin to heroin and prescription opioids like Opana. Most reports describe the abuse-deterrent properties as ORF becoming a gel or jelly when it is broken apart and water is added to it. Several reports state that people try to get around the abuse-deterrent properties by (b) (4) it and one report states that people have found a way to smoke it.

In Canada, an expert committee for the Atlantic Common Drug Review found that there was no evidence that OxyNEO (new OxyContin formulation marketed in Canada) was less addictive or harder to abuse than original OxyContin and quoted a pharmacy consultant as saying OxyNEO had no advantage over OxyContin if one used a coffee grinder.

Reviewer Comment: These reports are generally supportive of the study findings.

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/s/

BOB A RAPPAPORT
02/10/2013