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1. INTRODUCTION

The May 5, 2008 joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (the "Joint Committees") will discuss the appropriateness of including information about the characteristics and results of *in-vitro* testing in the Prescribing Information (PI) of appropriately tested controlled-release opioid products. Purdue Pharma L.P. (PPLP) appreciates the opportunity to present information on its newly formulated product and its position on this important issue to the Joint Committees and to hear the Joint Committees discussion and advice on the issue.

PPLP has submitted to the FDA NDA 22-272, an application for a newly formulated controlled-release oxycodone tablet (referred to as OTR throughout this document as it was used internally; the term is not intended for public use). This product has been shown, in our studies, to be bioequivalent to the currently marketed formulation of OxyContin[®] Tablets and has physical properties that provide resistance to certain methods used to defeat the controlled-release mechanism of the currently marketed formulation. The original NDA for OTR includes the 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg tablet strengths, and a supplemental NDA for the 60 mg and 80 mg tablets is planned for submission immediately after this NDA is approved. The physical properties of all tablet strengths have been rigorously tested in well-designed *in-vitro* studies which are summarized below. A summary of this data will be presented at the meeting on May 5, 2008. It is currently our plan that the OTR product will be marketed under the same trade name as the currently marketed product, OxyContin[®] Tablets.

PPLP has discussed this labeling issue with FDA and requested inclusion of information about the product's physical properties in the Prescribing Information (PI). Compromising the controlled-release mechanism of the currently marketed OxyContin formulation by crushing the tablet is the first step for a portion of the nonmedical use (NMU) of the product. The basis for reformulating this product was to make the process of defeating this mechanism more difficult. OxyContin Tablets were approved by FDA in 1995 and are considered a safe and effective medication when appropriately prescribed and used by patients as directed. Since their introduction, OxyContin Tablets have provided significant benefit to patients, but the product also has a history of being abused. This history has caused PPLP's research to focus on developing a product that would maintain the benefit of the product to patients while reducing the desirability to abusers.

Our pharmacokinetic studies indicate that OTR is bioequivalent to the currently marketed OxyContin Tablets formulation and, therefore, the differences in physical properties should not adversely affect the safety or efficacy of the product when taken as directed by patients. In addition, based upon the results of rigorously designed and conducted extraction studies, we believe the OTR formulation will present meaningful impediments to those who abuse the currently marketed product by defeating the controlled-release delivery system.

We believe that it is appropriate that when prescribing controlled substances physicians consider both the care of the patient and concerns for possible abuse. For that reason, we

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believe that it is important that the PI describes the tamper resistant characteristics of OTR. The considerations for labeling raise a number of issues for discussion. Why was this formulation change initiated? Is there a precedent for including such data? How will this information best be communicated? What value is this product expected to provide and how will that value be monitored? The inclusion of the *in-vitro* testing data in the prescribing information is supported by discussions in the following sections:

- Precedent for *In-vitro* Data and Nonclinical Information in the Prescribing Information (PI) of Other Products
- Risk Communication
- Product Background
 - Development of Tamper-resistant Properties
 - Review of the Literature and Surveys
 - Review of Information relative to Routes of Nonmedical Use (NMU) of OxyContin
 - Summary of Information on Routes of Abuse
- Product Information
- Clinical Pharmacology
- Summary of the *In-vitro* Testing and Results
- Impact of Ethanol on Intact Dosage Form Dissolution
- Proposed Labeling
- Potential Benefits and Planned Surveillance

2. PRECEDENT FOR *IN-VITRO* DATA AND NONCLINICAL INFORMATION IN THE PRESCRIBING INFORMATION (PI) OF OTHER PRODUCTS

The results of *in-vitro* testing are not routinely included in the Prescribing Information (PI) of prescription products. The exceptions include *in-vitro* sensitivity testing of anti-infective products and *in-vitro* mutagenicity testing and pharmacology testing in tissue cultures. In these examples, included data are generated using rigorous testing methods, and are accompanied by statements that place the *in-vitro* test results in perspective, indicating that they may not be predictive of *in-vivo* experience. Although not wholly predictive of *in-vivo* results, this information provides prescribers with a better understanding of the key attributes of the product and its proper use.

There are other cases where nonclinical information is provided as a means of helping physicians understand the characteristics of the product they are prescribing. Products with controlled-release mechanisms (tablets, capsules or transdermal delivery systems) may include information about the delivery system in the PI in order to help explain the physical properties and performance of the product. In these circumstances the nonclinical information is undeniably useful to physicians in understanding a product's attributes and how it may perform. Similarly, PPLP believes that the *in-vitro* extraction data will provide prescribers, pharmacists,

and other healthcare professionals with useful information about the characteristics of the controlled-release opioid product¹⁶.

There are examples of information in product PIs that discuss the chemical nature of a product and how it relates to abuse issues. In the PI of Lomotil, it states in the Drug Abuse and Dependence Section “... *The insolubility of diphenoxylate hydrochloride in commonly available aqueous media precludes intravenous self-administration.*”

In the PIs of certain prescription marketed products such as Vyvanse, there is information about clinical “liking” studies:

“In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dimesylate and 40 mg immediate release d-amphetamine sulfate were administered to individuals with a history of drug abuse, lisdexamfetamine 100 mg produced subjective responses on a scale of “Drug Liking Effects”, “Amphetamine Effects”, and “Stimulant Effects” that were significantly less than d-amphetamine immediate release 40 mg. However, oral administration of 150 mg lisdexamfetamine produced increases in positive subjective responses on these scales that were statistically indistinguishable from the positive subjective responses produced by 40 mg of oral immediate-release d-amphetamine and 200 mg of diethylpropion (C-IV). Intravenous administration of 50 mg lisdexamfetamine to individuals with a history of drug abuse produced positive subjective responses on scales measuring “Drug Liking”, “Euphoria”, “Amphetamine Effects”, and “Benzedrine Effects” that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.”

These studies provided information about the preferences of subjects who abuse these products. The “liking” studies were one way of providing information about abuse potential before the compound was marketed. However, long-term monitoring would still be needed to determine the true preference of the product by the nonmedical user community once it is on the market. This is not the case with older compounds like oxycodone that have been marketed in various dosage forms for many years. Evidence is readily available on the abuse of older compounds and abusers’ preferences. What is not available is how a particular formulation would perform when subjected to rigorous manipulation to extract the drug. This testing could be considered analogous to the “liking” studies involving a new chemical entity. It is understood that the protocols for “liking” studies have been developed over time and have become a relatively common inclusion in a the PI of certain drugs while the protocol and inclusion of *in vitro* extraction testing is a new concept for a PI. Similarly, this testing is not a substitute for long-term monitoring; however, the data provide useful information about a specific formulation.

3. RISK COMMUNICATION

PPLP believes that balanced risk communication is an important aspect of an effective risk management program. Prescribing Information is an important tool in providing prescribers with risk information about a product. The information should be as complete as possible within the limitations of the Prescribing Information format and provide prescribers with information needed to understand the product they may be prescribing. Products in other therapeutic classes that provide risk information allows for balanced information to be presented if there are data about a

particular product that distinguishes it. In the case of controlled-release opioids, abuse is an issue of great concern and information about the potential abuse of a product makes up a substantial part of the label for these products. Purdue believes that products that have undergone rigorous *in-vitro* extraction testing should have appropriate summary information for this testing included in the PI.

Although similar in appearance to the currently marketed formulation of OxyContin, the new formulation has subtle dimensional differences and different indicia, and patients and practitioners will be able to differentiate between the two formulations. Since patients are understandably concerned about how changes in their medication may affect their care, they are likely to ask their healthcare professionals about the differences. If appropriate information is not provided in the PI about the new formulation, it will be a difficult for prescribers and pharmacists to fully answer such questions. In a similar vein, sales representatives, who remain a primary source of product information for prescribers and who are required to strictly abide by regulatory guidance on promotion, would face insurmountable obstacles to explain the change without appropriate language in the PI. Since the PI has always served as the guidance for sales representative communications with prescribers and pharmacists, the absence of a clear description of the physical characteristics of the new formulation in the PI will likely not allow the company representative with the most regular contact to prescribers to explain any changes. If any deviation to this disallowance were to be made by the company providing information that is not included in the PI may result in a challenge by the FDA's Division of Drug Marketing, Advertising and Communication (DDMAC) or potential legal action because of "off-label" promotion. Therefore, in order for PPLP to be able to most effectively communicate this information, it needs to be included in the PI.

The complete data required to file an NDA were available for the OTR 10 mg-40 mg tablet strengths before all the required data on 60 mg and 80 mg tablet strengths. PPLP decided to submit the NDA for the 10 mg-40 mg strengths as soon as these data were available rather than wait to submit an NDA for all the planned tablet strengths in order to make the medication available to patients and the healthcare community in a timely manner. In this situation, a complete description of the physical differences between the formulations is even more important because different formulations will be available until the supplemental NDA for the 60 mg and 80 mg strengths is approved and the older formulation is replaced in the marketplace. Since an understanding of differences in tamper-resistant properties between formulations could be important to a physician's prescribing decisions, physicians should be aware of the different formulations and their physical characteristics.

As with all new products, the promotional material to be used at launch will be reviewed by DDMAC before it is used. After FDA approval, Company representatives will begin advising healthcare professionals of the new product using this reviewed material. While the ultimate goal is to replace the current formulation with the new formulation, PPLP will discuss OTR with healthcare professionals during the transitional period when both formulations are available. As patients may have questions about the new formulation, it is important that healthcare professionals are appropriately informed in this regard.

It is PPLP's intent to limit the dissemination of information by sales representatives regarding the physical and chemical properties of the new product to that agreed upon with FDA or included in

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the PI. We understand that these physical and chemical properties are defined by the *in-vitro* testing results. This information will be included in material that is discussed with, and provided to, healthcare professionals. We anticipate that questions will arise from these discussions; if they extend beyond the information provided in the PI, Company representatives will be instructed to forward these questions to the Company Medical Services Department.

4. PRODUCT BACKGROUND

4.1. Development of Tamper-Resistant Properties

The reason for the formulation change of OxyContin was to address the abuse of the product. The testing of the OTR formulation ranged from tampering methods considered “easy” or that involve “readily available” tools (including those associated with OxyContin abuse), to more sophisticated methods and tools.

For over a decade, PPLP has been pursuing the development of opioid analgesic products that benefit patients and reduce abuse. Although OTR is an important milestone in this regard, our research in this area is ongoing.

Productive discussions of this issue require a consistent use of clearly defined terms. The incorrect use of conceptually different terms as though they are synonyms can be a cause of confusion and may lead to a misunderstanding of the value of a product.

Abuse-proof products, those that cannot be abused in any manner, are not feasible at this time since products can be abused by simply taking one or more intact doses via the intended route. For modified-release formulations, the active drug substance must be “released” from the dosage unit to achieve its therapeutic effect. Therefore, the development of tamper-proof products, those that cannot be manipulated in any way to release drug faster than intended or cannot be prepared for any method of abuse, may not be technically feasible at this time without compromising efficacy in patients.

Tamper-resistant opioid formulations are designed to reduce the amount of opioid that can be made readily available for abuse upon tampering; they make it more difficult and time consuming to recover opioid from the formulation.

Another concept that should be defined is “drug abuse liability”¹⁷. For purposes of this document, it is defined as the risk or liability of a CNS-acting drug to sustain NMU that may result in disruptive or undesirable consequences. Regardless of the properties a formulation may have, the active substance will retain this liability. It is relevant to older products with new formulations since the issue is how to prevent extraction of the active drug substance for NMU.

In various academic and other forums, PPLP has described how the development of tamper-resistant products may be attainable by various technologies, including the addition of bioavailable or sequestered opioid antagonists, addition of aversive substances, or alteration of the physical and chemical properties of the formulation. PPLP believes that the unique characteristics imparted by each approach could successfully impede some, but not all,

methods of tampering. These important improvements may result in a change to the abuse profile of a product, compared to a prior formulation. However, it is difficult to predict *a priori* how formulation design may ultimately affect actual abuse once a product becomes available. The degree of translation of designed tamper resistance to actual lowered abuse can only be established by long-term observations once a product is on the market.

It is important that we understand how a prescription product is abused if we are to understand how a change to that product's attributes may affect the problem.

4.2. Review of the Literature and Surveys

The abuse of prescription opioid analgesics creates a significant health burden to the U.S.A. The National Survey on Drug Use and Health (NSDUH), conducted annually by the Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services, estimates the annual prevalence of NMU of various medicines as well as abuse of illicit substances.¹² Data from the 2006 NSDUH, the most recent publicly available source, indicate that the NMU of prescription psychotherapeutics (pain relievers, tranquilizers, sedatives and stimulants) is substantial. Approximately 49.8 million Americans aged 12 or older reported NMU of any psychotherapeutic at some point in their lifetimes, representing 20.3% of the population aged 12 or older. Nearly 7 million Americans aged 12 or older, or about 2.8% of the population, reported *current* (past month) use of psychotherapeutic drugs for nonmedical purposes. The table below summarizes some of the 2006 NSDUH data.

Table 4.2.a: Percent of Individuals 12 and Older Reporting *Past Month* Nonmedical Use (NMU) of Psychotherapeutics, 2006, by Age Category

	12-17	18-25	26 or older	12 or older
NMU Any Psychotherapeutic Med.	3.3	6.4	2.2	2.8
Pain relievers	2.7	4.9	1.5	2.1
OxyContin	0.1	0.4	0.1	0.1
Tranquilizers	0.5	2.0	0.5	0.7
Stimulants	0.6	1.3	0.3	0.5
Sedatives	0.2	0.2	0.2	0.2

Another source of information on use of medicines without a doctor's order is the federally-funded Monitoring The Future Survey (MTF). The MTF is administered annually to over 48,000 8th-, 10th- and 12th-grade students from 403 private and public schools nationwide selected to be representative of secondary school students in the coterminous United States.⁶ Data relevant to this discussion are presented in the table below.

Table 4.2.b: Percent of Students Reporting Annual NMU of Prescription Medicines, 2007, by Grade

	8 th Grade	10 th Grade	12 th Grade
Other Narcotics	n/a	n/a	9.2
OxyContin	1.8	3.9	5.2
Vicodin	2.7	7.2	9.6
Amphetamines	4.2	8.0	7.5
Ritalin	2.1	2.8	3.8
Sedatives	n/a	n/a	6.2
Tranquilizers	2.4	5.3	6.2

OTR was developed in response to concerns about the NMU of OxyContin Tablets. The following section summarizes currently available information on routes of NMU of OxyContin or of non-specified oxycodone-containing drug products.

4.3. Review of Information Relative to Routes of NMU of OxyContin

Interpreting the following data requires the understanding that they are derived from relatively specific subsets of nonmedical users. Therefore, it is not known if the available data represent the entire spectrum of NMU or the relative frequencies of route of abuse. For the tabular presentation of the data, all routes of abuse that have come to PPLP's attention are represented. Notably, although no study reported any participant attempting to vaporize the tablet with heat to inhale the vapors, a question about that route of administration was specifically included in one study. Some authors reported the route of administration for NMU as "oral" without specifying whether the person crushed or chewed the formulation prior to swallowing or whether the dosage form was swallowed intact. Authors also defined "use" and "nonmedical use" and "abuse" differently, so tables are titled to be consistent with the operational definitions employed by the authors. Throughout the text, the term "NMU" will be used for the sake of brevity and to encompass the spectrum of self-administration identified in these studies.

Three sources of information are presented in this summary: collected data reported in the literature specific to the NMU of OxyContin, a report of data obtained via an unrestricted grant from PPLP to Yale University by Loretta Grau and colleagues, and analyses focusing on the self-reported behaviors of those who also report OxyContin NMU in the National Survey on Drug Use and Health (NSDUH) and the Treatment Episode Data Set (TEDS), both of which are conducted annually under the auspices of the Office of Applied Studies, Substance Abuse and Mental Health Services Administration, Department of Health and Human Services.

4.3.1. Studies on Routes of Administration of OxyContin for Nonmedical Use

1) Carise D, et al.¹ conducted a study of 27,816 persons admitted for treatment at 157 addiction treatment programs in the United States from 2001 – 2004. Programs were located in 105 cities

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in 22 states, with 57% in urban areas. Males comprised 64% of the total sample and 42% of the total sample were white, with another 42% identifying as African-American. The mean age was 36 years (range: 18-87). Approximately 5% of the sample reported some prior use of OxyContin (referred to as “users”), with 86% of those reporting the motivation for NMU as being to “get high or to get a buzz” (referred to as “abusers”). Interestingly, the demographics of the abuser subset differed from the overall sample in that they were somewhat younger (mean age = 32 years, SD = 10) and 89% identified themselves as white. Routes selected by the abusers were not reported separately.

Table 4.3.1a: Routes, OxyContin Users (Including Abusers)

	Oral Intact	Oral Chewed	Oral NOS*	Intranasal	Injected	Smoked, Vaporized	Missing Data	Total
n (%)	NA*	NA*	981 (71.7%)	153 (11.2%)	234 (17.1%)	NR*	57	1425

* NOS = Not Otherwise Specified; NA = Not asked; NR = Not recorded/reported

In this report, at least 28.3% (*intranasal plus injected* divided by the number of subjects for which a route of administration was reported) of those admitting any use of OxyContin compromised the formulation as one step in preparing it for NMU. The report did not specify the manner of oral abuse, so the fraction of those engaging in oral NMU that compromised the formulation is not known.

2) Hays L, et al.⁴ conducted a retrospective chart review of admissions to the Addictive Disease Unit (ADU) in a free-standing, private psychiatric facility affiliated with the University of Kentucky from October 2000 – December 2001. The program’s catchment areas included metropolitan Lexington and rural Central and Eastern Kentucky. There were a total of 491 admissions to the ADU during the 15-month period, of which 258 were for opioid dependence (addiction) and formed the basis of the review. Of the 162 admissions (62.8%) that were primarily for abuse of or addiction to OxyContin, 148 (91.4%) were from a rural area. The majority of those abusing OxyContin were male (72.2%), 91.4% were white and the mean age was 31.5 years (SD = 10 years). The mean daily amount reported for NMU of OxyContin was 181.3 mg (range: 40-400 mg) and the mean duration of abuse was 19.7 months (range: 1-48 months).

Table 4.3.1b: OxyContin Route of Abuse, At Initiation of Abuse

	Oral Intact	Oral Chewed	Oral NOS*	Intranasal	Injected	Smoked, Vaporized	Missing Data	Total
n (%)	NRC*	NRC*	86 (82.7%)	17 (16.3%)	1 (1.0%)	NRC*	58	162

* NOS = Not Otherwise Specified; NRC = Not recorded in chart

Table 4.3.1c: OxyContin Route of Abuse, At Admission

	Oral Intact	Oral Chewed	Oral NOS*	Intranasal	Injected	Smoked, Vaporized	Missing Data	Total
n (%)	NRC*	NRC*	25 (21.4%)	68 (58.1%)	24 (20.5%)	NRC*	45	162

* NOS = Not Otherwise Specified; NRC = Not recorded in chart

At initiation, at least 17.3% of patients (*intranasal plus injected* divided by the number of subjects for which a route of administration was recorded) compromised the formulation. In contrast, by time of admission, at least 78.6% (*intranasal plus injected* divided by the number of subjects for which a route of administration was recorded) of this predominantly rural sample compromised the formulation prior to nonmedically using OxyContin. The charts did not indicate what proportion, if any, of those reporting the oral route crushed or chewed the tablets prior to ingestion. These results suggest a temporal change in the route of administration employed over the clinical course of NMU and abuse. Over time, some nonmedical users appear to transition from oral use to routes of self-administration that require compromise of the formulation.

3) Havens JR, et al.³ conducted a study in two rural, Appalachian counties in Kentucky using respondent-driven sampling. A sample of 184 persons was recruited between November 2004 and September 2005. Eligibility criteria included *any* use of OxyContin in the past three years and use of *any* opioid analgesic in the past 30 days either medically or nonmedically. NMU in this study was defined as having obtained the drug from a source other than a physician, a marked departure from the definition employed by SAMHSA in the National Survey on Drug Use and Health (NSDUH). The study cohort was predominantly white (98.4%) and 54.9% male. The median age was 30 years, with an interquartile range of 24-37 years. Since the investigators focused on injection drug use, no information on other routes of administration was reported.

Table 4.3.1d: OxyContin Route, At Interview

	Oral Intact	Oral Chewed	Oral NOS*	Intranasal	Injected	Smoked, Vaporized	Missing Data	Total
n (%)	NR*	NR*	NR*	NR*	47 (100.0%)	NR*	137	184

* NOS = Not Otherwise Specified; NR = Not reported

In this rural Kentucky sample, all the individuals met the authors' criterion for NMU of OxyContin, and at least 25.5% compromised the formulation prior to abuse.

4) **Grau LE, et al.**² used a respondent-driven sampling approach to survey OxyContin abusers residing in Cumberland County, ME (Portland area). The study was conducted during between July and September 2002 by researchers from Yale University's Department of Epidemiology and Public Health under a grant from PPLP. Males comprised 70.9% of the sample, and 87.8% identified themselves as non-Hispanic Caucasians. Median age was 27 years (range: 16-52).

Table 4.3.1e: Route, At Initiation of OxyContin NMU

	Oral Intact	Oral Chewed	Oral NOS*	Intranasal	Injected	Smoked, Vaporized	Missing Data	Total
n (%)	65 (30.4%)	18 (8.4%)	NA*	112 (52.3%)	19 (8.9%)	NA*	0	214

* NOS = Not Otherwise Specified; NA = Not asked

Table 4.3.1f: OxyContin NMU Route, At Time of Interview

	Oral Intact	Oral Chewed	Oral NOS*	Intranasal	Injected	Smoked, Vaporized	Missing Data	Total
n (%)	37 (17.6%)	8 (3.8%)	NA	119 (56.7%)	46 (21.9%)	NA*	0	210

*NOS = Not Otherwise Specified; NA = Not asked

At initiation of OxyContin NMU, 69.6% of respondents reported a route of administration that involved compromising the formulation (*chewed plus intranasal plus injected* divided by the total). In contrast, by the time of interview 82.4% reported a route of NMU that involved compromising the formulation (*chewed plus intranasal plus injected* divided by the total). These data suggest that over time, some nonmedical users transition to routes that require compromise of the formulation.

5) **Katz DA, et al.**⁷ described the case reports of three adolescents who admitted to OxyContin NMU, two of whom reported intranasal NMU and one who reported intravenous NMU.

In summary, nationally generalizable data on the prevalence of different routes of abuse of OxyContin are nonexistent. As the foregoing literature review shows, the data that do exist are limited, were derived from different samples of nonmedical users, and used different survey tools for eliciting information on routes of abuse. The largest and most geographically representative sample (Carise, et al.) indicates that, at a minimum, 28.3% of persons admitted to treatment programs were using OxyContin in a manner that involved compromising the formulation (intranasal and injection). At the time of evaluation in the studies reported above, the percentage of subjects who compromised the existing OxyContin formulation prior to NMU ranged from 28.3% to 82.4%. However, because of the variability across these studies in terms of sampling and data collection methods, time frames and geographic locale, it is not possible to determine definitively the true proportion of individuals who compromise the formulation for the purposes of NMU.

4.3.2. Analysis of 2006 NSDUH¹²

Analysis of the public user dataset for the most recently available data from NSDUH (survey year 2006) showed that 3,985,104 individuals aged 12 or older in the United States reported OxyContin NMU in their lifetime in 2006; 1,225,904 reported OxyContin NMU within the past year; and 281,733 reported OxyContin NMU within the past month (considered current NMU).

- Of those admitting OxyContin NMU in the *past year*:
 - 17.8 % reported ever using a needle to inject drugs.*
 - 6.6 % reported using alcohol or illicit drugs in the past 30 days.
 - 31.4 % reported heavy alcohol use in the past 30 days.
 - 66.3 % reported binge alcohol drinking (5 or more drinks on 1+ occasion) within the past 30 days.
- Of those admitting OxyContin NMU in the *past month*:
 - 27.2 % reported ever using a needle to inject drugs.*
 - 100 % reported using alcohol or illicit drugs in the past 30 days.
 - 34.2 % reported heavy alcohol use in the past 30 days.
 - 65.3 % reported binge alcohol drinking within the past 30 days.

*NSDUH does not ask which drugs are injected.

4.3.3. Analysis of 1996 – 2005 TEDS Data¹³

TEDS is one of the three components of SAMHSA's Drug and Alcohol Services Information System (DASIS). DASIS is the primary source of national data on substance abuse treatment. TEDS includes data from facilities that are licensed or certified by the State substance abuse agency to provide substance abuse treatment (or are administratively tracked for other reasons), and that are required by the States to provide TEDS client-level data.

The minimum data set required to be collected by TEDS includes information on the primary, secondary, and tertiary substances and their route of administration (specifically: oral, inhaled, injected, other/unknown).

All admissions reported to TEDS increased from 1,639,064 in 1996 to 1,847,515 in 2005. Admissions due to abuse of or addiction to “narcotic analgesics” increased from 32,829 to 119,920 over the same time. Admissions are further reported at the opioid drug substance level (ie, chemical entity) by 16 US jurisdictions (AL, DC, FL, GA, KY, MD, ME, MS, MO, NV, NH, NJ, NM, ND, OH and SC), but not at the drug product level (eg, OxyContin). Those admissions indicating oxycodone as the primary substance increased from 71 to 5,518. Data on route of abuse from these jurisdictions are presented below.

Table 4.3.3.a: Oxycodone NMU Route, At Admission, (Number, percentage)

	Oral Intact	Oral Chewed	Oral NOS*	Inhaled	Injected	Smoked, Vaporized	Other/ UNK	Total
1996	NR*	NR*	66 (93.0%)	3 (4.2%)	1 (1.4%)	NR*	1 (1.4%)	71
2005	NR*	NR*	2,633 (47.7%)	1,841 (33.4%)	942 (17.1%)	NR*	102 (1.8%)	5,518

* NOS = Not Otherwise Specified; NR = Not reported

Over the 10-year period, the percentage of individuals abusing oxycodone-containing products as their primary drug by means that involve formulation compromise (*inhaled plus injected*) increased from 5.63% to 50.43%.

4.4. Summary of Information on Routes of Abuse

In summary, information on routes of administration involved in the NMU of OxyContin is limited and may not adequately represent all the relevant populations who engage in OxyContin NMU.

Despite these limitations, a review of the available data yields several findings. Firstly, a proportion of those who engage in NMU of OxyContin choose routes of administration which require compromise of the formulation prior to abuse. Another common route of OxyContin administration for nonmedical use/abuse purposes appears to be oral self-administration of intact tablets. The OTR formulation will likely have no dissuading effect on those who abuse the drug via this route of administration. However, OTR was designed primarily to frustrate those who chew or crush tablets prior to swallowing, those who crush tablets and inhale the resultant powder, and those who crush tablets, dissolve the powder and inject it.

Secondly, these data suggest that preferences for route of administration for NMU of OxyContin may be dynamic and a function, at least partially, of the length of time an individual has been nonmedically using the substance. If the OTR formulation offers a sufficient barrier to transitioning from oral-intact abuse to other methods that require compromise of the formulation, a public health benefit may thereby be realized.

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Thirdly, the NSDUH data indicate that a sizeable proportion of people admitting to NMU of OxyContin also consume alcoholic beverages in patterns that most healthcare professionals would consider unhealthy. The OTR formulation's resistance to dose-dumping in the presence of ethanol may impart a safety measure in the population engaging in NMU and unhealthy ethanol consumption.

While the nationally representative number of nonmedical users who employ nonoral routes of self-administration of opioid analgesics may be difficult to determine with precision, it appears to be a meaningful number, and such individuals are at increased risk for addiction and a host of other adverse medical, economic and legal outcomes (eg, engaging in illegal activities to obtain drugs, simultaneous polydrug abuse, medical problems as a direct result of drug abuse, transmission of infectious diseases by sharing needles).^{5,8,10,11,14,15} As a result, nonoral abusers likely constitute the most costly group of nonmedical users from a societal perspective.

5. PRODUCT INFORMATION

Since the primary purpose of an analgesic is to help manage the pain experienced by patients, the primary objective of this reformulation project was to develop a tamper-resistant tablet that was bioequivalent to the current formulation of OxyContin Tablets. The intended indication, patient population, and methods of use remain the same as for the original formulation.

PPLP has submitted to FDA an NDA that meets those objectives. As previously stated, we do not believe OTR is an abuse-proof or tamper-proof product. We view its physical properties as an important improvement that will provide patients with a safe and effective analgesic that is therapeutically interchangeable with the current OxyContin product, but one that will present significant barriers to tampering.

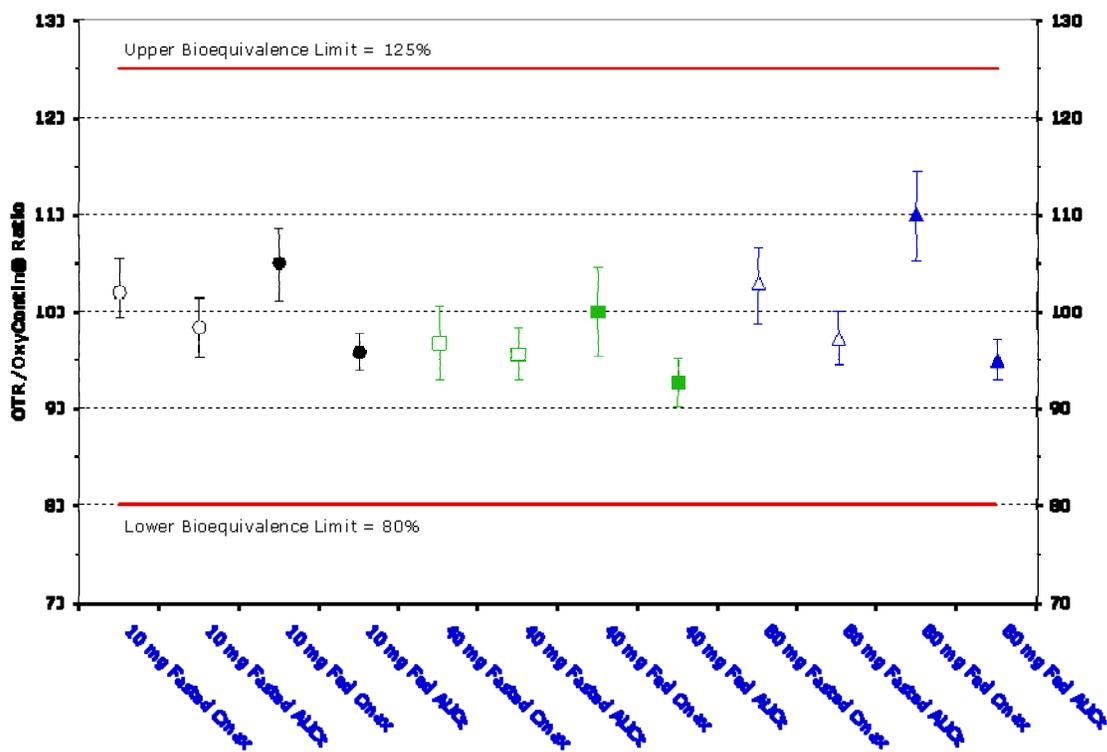
The new formulation consists of a controlled-release tablet covered by a cosmetic film coat. The film coat is colored for identification purposes. The uncoated tablets for all strengths have the same qualitative composition. The composition includes a polymer used previously in approved tablet formulations. During the manufacturing process the controlled-release uncoated tablet is heated above the melting point of the polymer. On cooling, the polymer within the uncoated tablet fuses to impart plastic-like properties to the tablet. The resistance of this product to chemical and physical manipulation has two aspects, both directly related to the presence of the polymer, and are described below.

The tablets are difficult to break using methods typically employed by drug abusers. Even when tablets are broken, they tend to fracture into comparatively large fragments, instead of small pieces or powder. These fragments retain some degree of controlled-release properties, as demonstrated in *in-vitro* dissolution testing, such that the entire active ingredient contained therein does not become immediately available. In addition, when exposed to many solvents the polymer becomes a gelatinous mass that impedes aspiration of the active ingredient through a needle into a syringe.

5.1. Clinical Pharmacology

PPLP pivotal bioequivalence studies have demonstrated that the new OTR formulation is bioequivalent to the currently-marketed OxyContin formulation under both fasted and fed conditions. As shown in Figure 5.1a, the 90% confidence intervals for the ratios of maximum concentration (C_{max}) and total exposure (AUC) for OTR vs. currently marketed OxyContin all lie within the 80 to 125% interval that defines the regulatory standard for bioequivalence. Additional pharmacokinetic studies demonstrated dose proportionality across the range of OTR tablet strengths.

Figure 5.1a: OTR vs. OxyContin Bioequivalence Summary Results (LS mean ratios with 90% Confidence Intervals)



5.2. Summary of the In-vitro Testing and Results

The purpose of the *in-vitro* testing protocol was to evaluate a wide range of physical and chemical methods intended to compromise the controlled-release mechanism of the reformulated product. The series of tests was designed to simulate methods which could be used by those intending to defeat the controlled-release mechanism prior to using the product for nonmedical purposes. The protocol used by PPLP incorporates a series of tests which, when used to evaluate different products, allows for comparison of the data. The protocol in use at the current time has evolved over several years of working with “tamper-resistant” products and includes tests to evaluate what PPLP considers to be a wide range of methods for defeating

the controlled-release mechanism of the product under test. The range of tests extends from those considered relatively simple to perform to those requiring advanced planning, mechanical equipment, multiple steps for extraction of the active drug substance, and solvents not typically available to the general public.

In-vitro testing, according to the protocol submitted to FDA by PPLP on 21 Dec 2006, was conducted on each of the seven strengths of OTR (10 mg to 80 mg) and one batch of each of the seven currently marketed strengths of OxyContin Tablets (10 mg to 80 mg). The detailed results of these tests were filed as part of the NDA. (The data presented here are a summary of that included in the filing.) The testing covered a wide range of possible extraction methods, from relatively simple to sophisticated methodology. The results need to be considered within the context of the formulation's therapeutic activity, ie, the intact product must release the opioid in order to perform as an analgesic. As the following data are reviewed, it should be remembered that the total amount released in the testing includes the amount that would normally be released from an intact tablet at that time point.

The following text presents and compares the relative results obtained for the two sets of formulations. Tables are used, as appropriate, to provide clarity. In these tables, the data presented are the range of values obtained for all strengths of OTR and OxyContin.

5.2.1. Crushing/Milling

The data presented in Sections 4.2 to 4.4 noted that a proportion of nonmedical users of opioid analgesics tamper with the product to defeat the controlled-release mechanism prior to abusing the product. In the case of oral abuse, this may be as simple as chewing the tablets. For IV abuse, crushing (to achieve particle size reduction and, therefore, increase surface area) is utilized to facilitate more rapid extraction into a small volume of water suitable for injection. Similarly, preparation for intranasal abuse involves crushing to reduce particle size to facilitate nasal insufflation and to defeat the formulation's controlled-release mechanism. An increased resistance to crushing should therefore be a significant attribute in reducing the potential for abuse of a controlled-release opioid by those who crush the tablets as a precursor to abuse. As stated in the description of the formulation, OTR tablets have plastic-like properties which make them difficult to break. Even if some degree of size reduction is achieved, this does not result in a fine powder, and, moreover, some controlled-release properties are retained. This attribute was demonstrated during a series of crushing and milling tests.

5.2.1.1. Crushing Manually

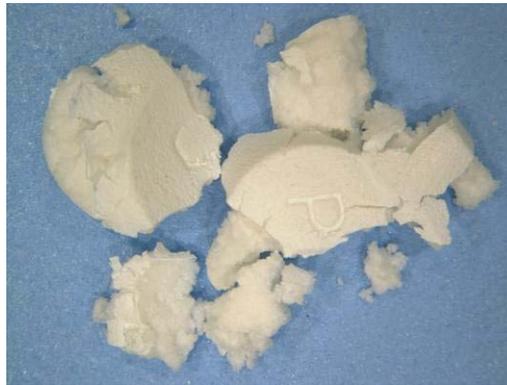
After crushing manually, dissolution testing was performed for each strength of OTR and the current OxyContin tablets. The OTR tablets were difficult to crush manually, resulting in large fragments and no powder.

Figure 5.2.1.1a shows the impact of crushing manually on representative OxyContin and OTR tablets, depicting the coarse fragments remaining for the OTR product.

Figure 5.2.1.1a: Representative Images of Manually Crushed Tablets



Crushed OxyContin



Crushed OTR

The large fragments retained some of the controlled-release properties of the original tablet and less than half of the oxycodone (20-49%) was released using dissolution apparatus (approximately 19% is released from an intact tablet under the same test). OxyContin tablets were easily reduced to a fine powder, resulting in release of 91% or more of the oxycodone after the same dissolution test. These data are presented in Table 5.2.1.1b.

The application of pressure between 2 spoons is a typical method used by nonmedical users of opioids in order to prepare the dosage form for extraction of the active ingredient. OxyContin tablets were readily crushed to a fine powder in this manner, but OTR tablets were relatively unaffected and remained intact. Additional tools, planning, and time would be needed to crush the OTR tablets.

Table 5.2.1.1b: Crushing Manually

	Crushed Manually. % Label Claim released after dissolution	Break when crushed with 2 spoons
OTR 10-80mg.	20-49%	No
OxyContin 10-80mg	≥91%	Yes

5.2.1.2. Milling

The testing summarized in Section 5.2.1.1 demonstrated the difficulty in crushing the OTR tablets. This section summarizes the results obtained when the size reduction of the tablets was undertaken with a more aggressive method. Using a mechanical mill as part of the process to defeat the controlled-release system represents an incremental increase in the planning and equipment required as well as placing limitations on the locations where tampering can be performed.

The seven strengths of OTR tablets were separately ground. Material equivalent to one tablet was analyzed by dissolution testing. Since the use of a mechanical mill was considered an increase in complexity and as OxyContin tablets were easily rendered into a powder with manual crushing; the use of a mechanical mill was not required with the currently marketed OxyContin formulation. OxyContin tablet crushing data from Section 5.2.1.1 were used for comparison.

Thirty-six to 52% of oxycodone was released by dissolution testing from the milled OTR tablets as compared to 91% or more released after crushed OxyContin tablets.

Figure 5.2.1.2a shows representative images of milled OTR tablets before and after dissolution. This figure illustrates the ineffectiveness of producing a powder using a mechanical mill for the OTR tablets as compared to manually crushing for OxyContin tablets, as well as the gelling of the OTR tablet matrix during dissolution.

Figure 5.2.1.2a: Representative Images of Milled OTR Tablets Before and After Dissolution



Milled OTR

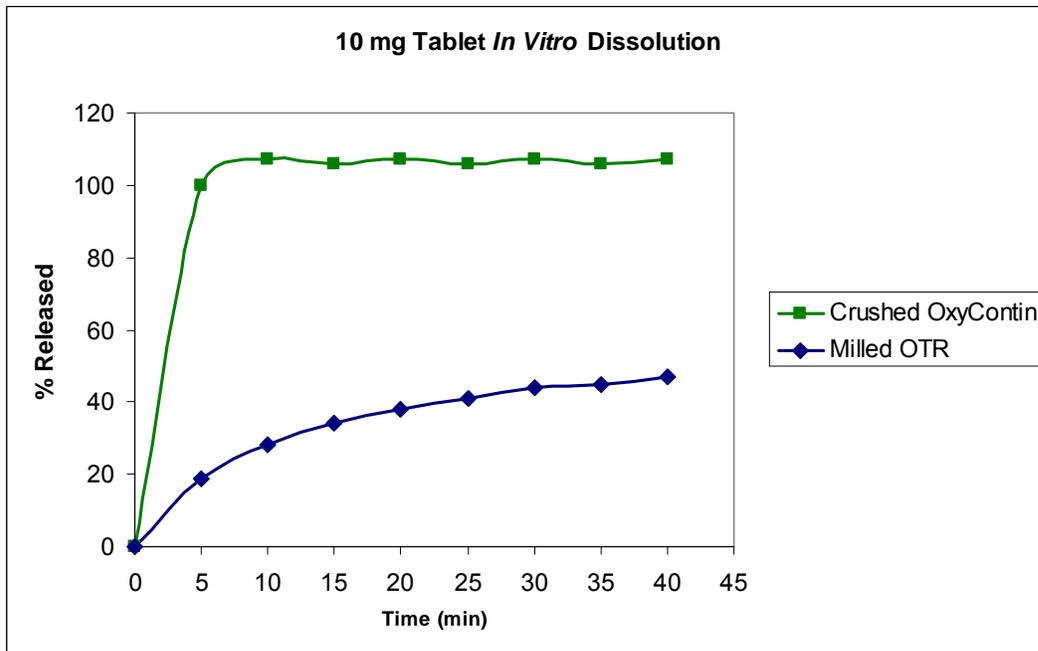


Milled OTR after Dissolution

Additionally, the relative dissolution rates of milled OTR tablets and crushed OxyContin tablets are shown in Figure 5.2.1.2b. Dissolution samples were collected every five minutes from T = 0 to T = 40 minutes for milled OTR 10 mg tablets and crushed OxyContin 10 mg tablets. Approximately half of oxycodone was released by dissolution testing from milled OTR tablets, but at a gradual rate that is consistent with a controlled-release product. The rate of release from milled tablets was only approximately twice that from intact OTR tablets. (Approximately

19% is released from an intact tablet). Conversely, dissolution of crushed OxyContin tablets results in almost complete release of oxycodone at the 5-minute sample time point.

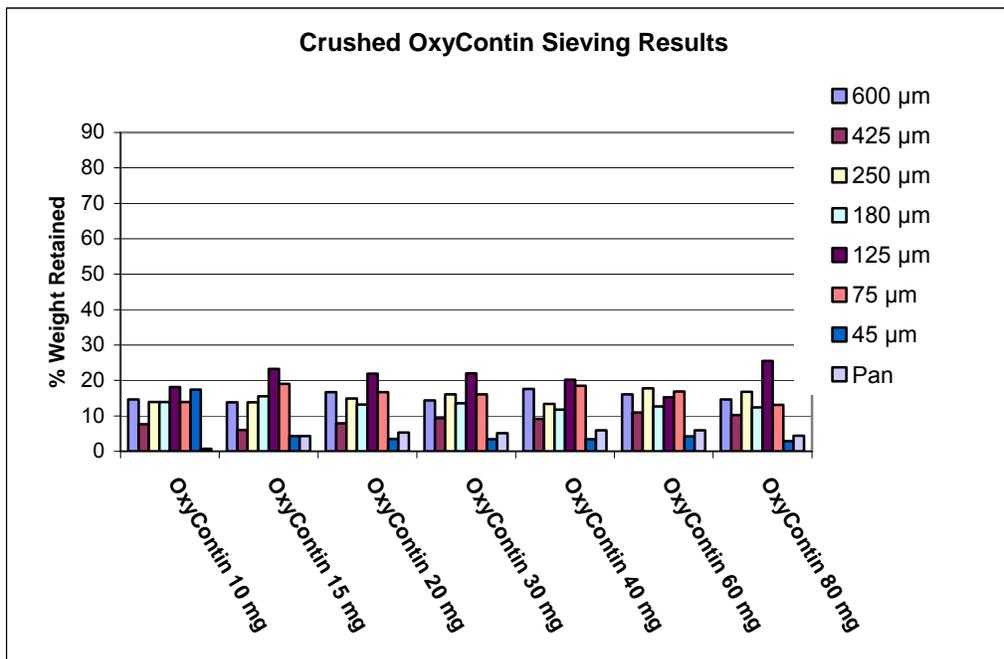
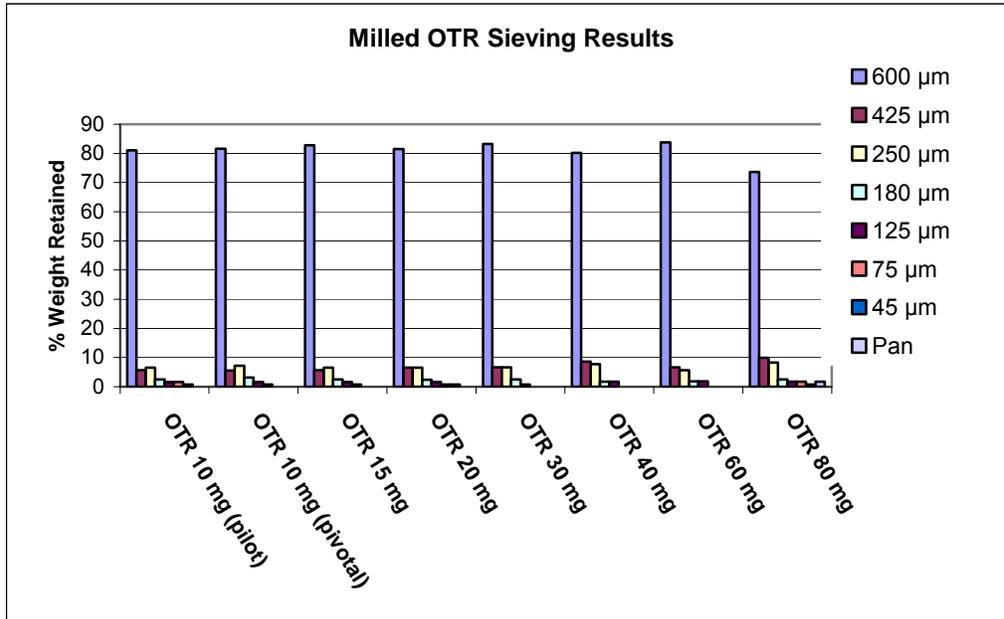
Figure 5.2.1.2b: Dissolution Curves for milled OTR and crushed OxyContin Tablets



5.2.1.3. Particle Size Distribution of Milled and Crushed Tablets

Milled OTR tablets and crushed OxyContin tablets were analyzed by sieving to evaluate the particle size distribution of the material. The material was sieved using mechanical vibration. As shown in the particle size distribution graphs in Figure 5.2.1.3 a/b, the largest particles, ie, those retained by a 600 µm-screen, comprised 74 - 84% of the intact OTR tablet weight. The large particle size and the retention of the controlled-release properties of the milled material are anticipated to dissuade nonmedical users from snorting the product. Crushing OxyContin tablets resulted in a much smaller particle size distribution.

Figures 5.2.1.3 a/b: Particle Size Distribution Graphs of Milled and Crushed Tablets



5.2.1.4. Simulated Preparation for Intravenous Abuse

OTR Tablets were milled (as per Section 5.2.1.2) and material equivalent to one tablet was placed onto a spoon. As previously stated, OxyContin tablets were easily and efficiently

crushed into a powder; therefore this method was used. Water was added to each spoon to extract the active ingredient or dissolve the drug product.

The milled OTR tablets became viscous after the water was added which resulted in a small amount (<0.3 mL) of the liquid being drawn into a syringe and analyzed for oxycodone content. Minimal amounts (1-4% Label Claim) of oxycodone were recovered. Approximately half (49-58%) of oxycodone was recovered from the crushed OxyContin tablets.

Figure 5.2.1.4a illustrates the gelling of the milled OTR tablet material when moistened, which is anticipated to be a barrier to IV abuse.

This *in-vitro* study demonstrated the resistance of the OTR formulation to extraction of oxycodone for IV abuse. Intravenous abuse is associated with a higher risk of immediate lethal outcome than other routes of abuse, and is attended by other health risks, such as cellulitis from injection technique, pulmonary emboli from inadvertent injection of particulate matter, and the transmission of infectious diseases (eg, hepatitis, HIV/AIDS, sepsis) from sharing needles. Intravenous abuse ranged from 17.1% to 21.9% of all NMU routes reported in the studies in Section 4. Therefore, the resistance of OTR tablets to IV abuse represents a noteworthy formulation improvement.

Figure 5.2.1.4a: Representative Images of Simulated IV Preparation



Milled OTR



Milled OTR after addition of water

5.2.2. Extraction Studies

The extraction studies conducted to evaluate OTR represented a progression from simple extraction with equipment and solvents readily available to the general public and short extraction times at room temperature, to more advanced extraction requiring more planning, less available or more harmful solvents, and longer extraction times at higher temperatures.

5.2.2.1. Simple Extraction – short duration/readily available simple solvents

Samples of each strength of OTR and OxyContin Tablets were manually crushed and vigorously shaken for a short period of time with five simple solvents at room temperature. As previously stated, OTR tablets were difficult to crush manually, whereas OxyContin tablets were easily reduced to a fine powder.

All strengths of OxyContin tablets released 89% or more of label claim in all solvents except the Simple Solvent 4. Simple Solvent 4 was not an effective solvent for this extraction. In the four solvents which gave good extraction results for OxyContin, each strength of crushed OTR formulation tested was shown to release $\geq 39\%$ less than the corresponding strength of crushed OxyContin tablets.

The ranges obtained for the formulations in each solvent are shown in Table 5.2.2.1a.

**Table 5.2.2.1a: Simple Extraction Results (Crushed Tablets)
% Label Claim Oxycodone Released for a Short Period of Time**

Sample – OTR/OxyContin	% Label Claim Released (range)				
	Simple Solvent 1	Simple Solvent 2	Simple Solvent 3	Simple Solvent 4	Simple Solvent 5
OTR 10-80 mg (crushed)	8-51	5-40	11-54	0-6	6-50
OxyContin 10-80 mg (crushed)	89-101	91-107	94-102	12-79	89-99

5.2.2.2. Extraction – Milling/Additional Solvents

This series of tests evaluated extraction from OTR tablets following milling. The solvents used were generally more harmful than those used in the simple extraction studies.

Milled OTR tablets and crushed OxyContin tablets were vigorously shaken for a short period of time with three medium solvents that is more complex than the Simple Solvents listed in section 5.2.2.1 at room temperature.

All strengths of crushed OxyContin released a minimum of 96% label claim in the Medium Solvent 1 and 94% label claim in the Medium Solvent 2. The Medium Solvent 3 was not an effective solvent to use for this extraction.

The milled OTR tablets released less than the crushed OxyContin tablets in all of the solvents. In Medium Solvent 1, the milled OTR tablets released between 26% and 52% less oxycodone than the corresponding OxyContin tablet strength. In Medium Solvent 2, the amount of oxycodone released from the OTR tablets was between 27% and 50% less than the corresponding strength of OxyContin.

Table 5.2.2.2a. Extraction Results % Label Claim Oxycodone Released for a Short Period of Time

Sample – OTR, <i>OxyContin</i>	% Label Claim Released (range)		
	Medium Solvent 1	Medium Solvent 2	Medium Solvent 3
OTR 10-80 mg (milled)	48-75	45 -71	14-27
OxyContin 10-80 mg (crushed)	96-101	94-98	16-53

5.2.2.3. Advanced Extraction (longer time and/or elevated temperature)

The next series of extraction studies evaluated a wider range of solvents and the use of extended extraction times and elevated temperatures.

As for the previous extraction study, OTR tablets were milled mechanically and the OxyContin tablets were crushed manually. The milled and crushed tablets were then vigorously shaken for an extended period of time in Simple Solvent 2, Simple Solvent 4, all three Medium Solvents, and additional more complex solvents at room temperature (RT). Additionally, the milled and crushed tablets were extracted in several of these solvents at elevated temperature for an extended period of time.

Complete extraction of the active ingredient from crushed OxyContin tablets was achieved using Simple Solvent 2, Medium Solvent 1 and Medium Solvent 2 after a short period of time at room temperature (Tables 5.2.2.1a and 5.2.2.2a). Therefore, longer extraction times and higher temperatures were unnecessary for these solvents and data for crushed OxyContin presented previously were used in Tables 5.2.2.3a and 5.2.2.3b.

The amount of oxycodone extracted from milled OTR tablets after extended period of time in Simple Solvent 2 at room temperature ranged from 29% to 65% less than the amounts extracted from the corresponding strengths of crushed OxyContin tablets after a short period of time at room temperature. Similarly, the amount of oxycodone extracted from milled OTR tablets after extended period of time in Medium Solvent 1 at room temperature ranged from 7% to 39% less than the amounts extracted from the corresponding strengths of crushed OxyContin tablets after a short period of time at room temperature; and the amount of oxycodone extracted from milled OTR tablets after extended period of time in Medium Solvent 2 at room temperature ranged from 17% to 61% less than the amounts extracted from the corresponding strengths of crushed OxyContin tablets after a short period of time at room temperature.

Complex Solvent 4 and Complex Solvent 5 were not effective extraction solvents for either formulation. As stated in Section 5.2.2.2, Medium Solvent 3 was also not an effective solvent to use for this extraction.

Complex Solvent 1 was the most efficient extraction solvent tested for the OTR formulation. Even in this solvent, the mean difference in % oxycodone extracted from the OTR formulation was 22% lower than the amount extracted from the corresponding strength of the current OxyContin formulation. Extraction methods employing Complex Solvent 1 as the solvent would

require a second extraction step in order to prepare an aqueous solution for injection or ingestion.

Extraction at elevated temperatures did not increase the release of oxycodone for milled OTR tablets due to the increased solubility of the tablet matrix at higher temperatures in most of the solvents tested. The increased solubility resulted in the tablet matrix becoming gelatinous.

Tables 5.2.2.3a and 5.2.2.3b contain average extraction amounts (% Oxycodone) for all samples tested at room temperature and elevated temperature, respectively.

Table 5.2.2.3a: Advanced Extraction Results % Label Claim Oxycodone Released with extended extraction time and Room Temperature

Sample – OTR/OxyContin	% Label Claim Released (range)				
	Simple Solvent 2	Medium Solvent 1	Medium Solvent 2	Complex Solvent 1	Complex Solvent 2
OTR 10-80 mg (milled)	32-78	61-89	35-80	62-103	22-66
OxyContin 10-80 mg (crushed)	91-107	96-101	94-98	95-102	95-103

Sample – OTR/OxyContin	% Label Claim Released (range)				
	Simple Solvent 4	Medium Solvent 3	Complex Solvent 3	Complex Solvent 4	Complex Solvent 5
OTR 10-80 mg (milled)	2-9	27-39	12-60	5-25	2-11
OxyContin 10-80 mg (crushed)	14-42	30-53	40-82	10-30	4-26

Table 5.2.2.3b: Advanced Extraction Results % Label Claim oxycodone Released with extended extraction time and elevated temperature

Sample – OTR/OxyContin	% Label Claim Released (range)						
	Simple Solvent 2	Medium Solvent 1	Simple Solvent 4	Medium Solvent 2	Complex Solvent 2	Complex Solvent 1	Complex Solvent 4
OTR 10-80 mg (milled)	34-68	53-78	0-7	57-70	21-74	51-78	9-39
OxyContin 10-80 mg (crushed)	91-107	96-101	19-38	94-98	95-103	95-102	16-37

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5.2.3. Thermal Treatment

Milled OTR tablets and crushed OxyContin tablets were added to a certain amount of solvent, heated to boiling and the liquid was analyzed for oxycodone content. OTR tablets released 21-48% (label claim) less oxycodone than the corresponding strength of OxyContin tablets.

5.2.4. Impact of Ethanol on Intact Dosage Form Dissolution

Dissolution testing was conducted on all strengths of OTR tablets using simulated gastric fluid with a range of ethanol concentrations up to 40% v/v. These tests showed no increase in dissolution rate for OTR tablets in ethanol concentrations of up to 40% v/v.

The OTR tablets, like the currently marketed OxyContin tablets meet the definition of a “rugged” formulation as described in the FDA presentation at the Advisory Committee for Pharmaceutical Science ACPS Meeting on 26 Oct 2005.

6. PROPOSED LABELING

The new formulation was evaluated in a series of rigorous *in-vitro* tests that were designed to defeat the controlled-release mechanism. The testing advanced from routine methods with easily available tools to more sophisticated methods employing chemicals and skills not possessed by most people. The testing demonstrated that when attempts were made to crush or mill the OTR tablets, the tablets either remained relatively intact or broke into coarse fragments that retained some controlled-release characteristics. When in contact with aqueous media, OTR tablets or fragments formed a gelatinous mass. As compared to the currently marketed OxyContin formulation, OTR exhibited considerable improvement with regard to resistance to most physical and chemical manipulation testing.

We initially considered several options concerning this information. One approach would be to not mention the testing data in the PI. However, as we discuss in this document, we believe that this information is important for prescribers and should be available to them. Therefore, we propose language that informs healthcare professionals of the formulation’s tamper-resistant characteristics.

The proposed wording in the NDA is similar to the following paragraph:

OxyContin 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg Tablets are an eroding matrix formulation of oxycodone hydrochloride where the release of the drug is controlled by the matrix. The dosage form consists of a controlled-release tablet covered by a cosmetic film coat. During *in-vitro* testing, tablets were manipulated to recover oxycodone by crushing, milling, heating, and crushing followed by boiling and filtering fragments, and crushing followed by extracting with various solvents, including ethanol. The tablets either did not break or broke into fragments that retained some of the controlled-release characteristics. When in contact with small volumes of aqueous media, the tablets or the fragments formed a gelatinous mass that could not be aspirated through a needle.

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7. POTENTIAL BENEFITS AND PLANNED SURVEILLANCE

After discussions with FDA, we were asked to provide some thoughts on the possible value of OTR and how we intended to monitor the product if it is marketed. We believe OTR will have a number of subtle and obvious positive effects. There is no assurance that all of the benefits described will be realized; we will be monitoring the product in the marketplace to evaluate its impact. Once approved for marketing, we plan to conduct a long-term epidemiological study and gather other information from our risk management program to more definitively assess formulation-based benefits to patients and any changes in abuse patterns.

Information we have generated in clinical studies indicates that the new formulation meets bioequivalence standards compared to the currently marketed OxyContin Tablets. As a result, OTR is considered to be therapeutically interchangeable with the currently marketed formulation.

The results of the rigorous *in-vitro* testing program that was designed to simulate methods of preparing the formulation for abuse provide evidence that the new formulation possesses physical properties that impart substantial resistance to specific methods of tampering. The new formulation is difficult to crush, so that simple, impulsive methods of tampering using two spoons or a bottle will not be as successful as with the current formulation. After such attempts, the resultant material is expected to be undesirable for nasal insufflation (snorting). The tampered product will form a gel if mixed with a small volume of water which is anticipated to introduce a significant barrier to NMU via injection. The resistance of the formulation to dose-dumping upon exposure to ethanol may dissuade those who would drop a tablet into an alcoholic beverage prior to ingestion, anticipating a significant rapid release of oxycodone. The new formulation may also provide a safety margin to those who ingest intact tablets for NMU while also consuming ethanol.

As is the case with any controlled substance, there undoubtedly will be those who abuse OTR by ingesting one or more intact tablets without a legitimate medical purpose. Such abuse is not thwarted by the new formulation, since the active drug substance must be released from the formulation for it to provide any analgesic effect.

The unknown variables regarding abuse methods, patterns, and subpopulations make projected benefits to nonpatients somewhat uncertain. One unknown variable is the actual fraction of persons who will attempt to compromise the integrity of the new formulation prior to abusing, compared to that fraction that will ingest intact tablets. Other unknown factors include determining whether the magnitude of the barrier to crushing is sufficient to dissuade a significant portion of abusers from choosing this formulation; whether methods for defeating the protections of the new formulation to make abusing it desirable to some segment of the nonmedical user population will be developed and disseminated to a meaningful extent; whether those who are frustrated by the formulation's features choose to seek rehabilitation instead of moving to a different licit or an illicit opioid; whether abusers frustrated by the formulation will choose a different route of administration that may carry less attendant risk of other medical problems; and whether the difficulty in crushing and extracting active ingredient will pose

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sufficient barrier to prevent some fraction of potential abusers from initiating abuse, or some number of abusers from progressing from oral to intranasal or injection drug abuse. Possible secondary benefits that may be associated with the new formulation include patient protection in settings where the tablet is chewed or crushed without the intent to abuse, situations in which a patient or a caregiver attempts to cut a tablet in two to make a prescription last longer than intended or to reduce the dose, and the prospect of a longer window for recognition of a problem and emergency care or resuscitation in the case of inadvertent ingestion by a toddler, who will not be able to chew a tablet made with the new formulation prior to swallowing and, therefore, will not be exposed to a complete or partial immediate release of oxycodone. Additionally, there may be continued patient safety due to the relative ethanol insensitivity which may reduce the likelihood of adverse reactions when the new formulation is ingested in temporal proximity to consumption of alcoholic beverages (although nothing in the formulation precludes additive effects of ethanol and the release of oxycodone as intended). Until such time as data are available, it is premature to state that the demonstrable tamper-resistant properties of the new formulation will translate into meaningful abuse deterrence with measurable public health benefits. PPLP intends to monitor the performance of the new formulation after approval by a number of methods that will provide near-, intermediate- and long-term information regarding the benefit/risk ratio to patients and society.

The surveillance activities for this product will rely on established programs PPLP has initiated and maintained in the Risk Management Program for OxyContin Tablets as well as new concepts for monitoring prescription drugs. Upon product launch, we will monitor OTR abuse on an ongoing basis using several sources of information. These will include data from the RADARS® System, Internet “chat rooms”, media reports, and listings from the National Association of Drug Diversion Investigators, Inc. list serve. In addition, we will examine trends in abuse of OTR over the long term in two ways: 1) via an internet survey of drug abuse information websites and, 2) a long-term epidemiological study of patterns of drug abuse among persons being admitted to drug treatment programs.

Other sources that will be monitored for long-term effects of this product include the NSDUH, TEDS and the Drug Abuse Warning Network (DAWN). PPLP believes that this surveillance plan will provide useful, temporally relevant information about patterns of OTR abuse which consequently serves to dynamically inform the product’s benefit/risk ratio.

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