PURDUE PHARMA L.P.

RESEARCH & DEVELOPMENT

September 24, 2009

FDA Advisory Committee Briefing Document on NDA 22-272 (reformulated OxyContin® tablets)

Summary of Briefing Document

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Context

OxyContin® (oxycodone HCl controlled-release, referred to as "OxyContin" through out this document) was approved by the FDA in 1995 for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Despite bringing important benefits to patients, problems with misuse, abuse and diversion of OxyContin began to emerge in the late 1990s, sometimes with fatal consequences in both knowledgeable addicts and recreational abusers. The current OxyContin formulation has specific unforeseen vulnerabilities that allow the product to be converted easily and rapidly (e.g., between two spoons or under a coffee mug) into an essentially immediate-release form that can be ingested via multiple routes. To mitigate this problem, Purdue began development of a modified-release, single-entity, reformulation of OxyContin that is bioequivalent to the current formulation but contains a different inert excipient (polyethylene oxide).

Purdue submitted an NDA for this therapeutically equivalent reformulation of OxyContin to FDA on November 29, 2007 (referred to as "reformulated OxyContin" and "the reformulation" throughout this document). Specific elements of the original NDA 22-272 were discussed on May 5, 2008 at a combined meeting of the Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committees. On October 3, 2008 Purdue received a Complete Response Letter from FDA that contained requests for specific additional physicochemical testing of the reformulated tablets. On March 30, 2009 Purdue submitted these additional data to FDA. This NDA is an application for a bioequivalent reformulation of OxyContin without any request for label claims regarding the potential benefits of the [redacted] formulation [redacted] accidental misuse or abuse.

Purpose of this document

This document serves to brief members of the CDER Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in advance of the September 24, 2009 joint meeting on reformulated OxyContin. This meeting will be the second Advisory Committee meeting on reformulated OxyContin, and will focus on

considering whether the *in vitro* data in the March 30, 2009 NDA resubmission are sufficient to satisfy the concerns raised in FDA's October 3 2008 Complete Response Letter. Based upon guidance from FDA the scope of this document is restricted to presentation of *in vitro* data that demonstrate the physicochemical differences between the current and reformulated OxyContin tablets. Risk evaluation and mitigation strategies (REMS) for this product are not included in this document as this topic is the subject of a separate discussion with FDA.

Overview of *in vitro* experimental studies

Purdue consulted independent experts in drug abuse and tablet tampering (see **Appendix I**) to guide and supervise the design, execution, analysis and interpretation of the new *in vitro* testing program. In designing these experiments, our goals were to

- First, evaluate the performance of the reformulation in response to various forms of physical and chemical manipulation to identify the incremental improvements it offers, and
- Second, confirm that [redacted] than the current formulation under any anticipated abuser tablet manipulation scenarios.

The experimental protocols assessed both the performance and limitations of this reformulation [redacted]. These protocols encompass seven groups of studies (represented below as Studies 1 – 7) that collectively test a wide range of anticipated abuser manipulations that require different amounts of time and effort input. They [redacted] to ensure consistency and reproducibility of results. The vast majority of the experiments were performed by contracted independent third party vendors. Personnel performing the experiments were blinded to the extent possible. The scientific rigor and scale of these *in vitro* studies maps the terrain of the potential outcomes of abuse and misuse to an unprecedented level. The availability of these data in turn enables future hypothesis-driven risk evaluation and mitigation strategies.

Study 1: (b) (4) Fractionation of Tablets

This study was designed to survey the number of techniques that could be employed to mechanically alter OxyContin formulations. The goal of these experiments was to broadly identify and characterize for the purposes of standardization of experiments, the methods and outputs that could be used for further physicochemical testing.

Tablets of reformulated OxyContin were more resistant to physical crushing techniques to reduce particle size than current OxyContin tablets, (b) (4) (b) (4) These tablets could when significantly more time or effort necessary to crush OxyContin was applied. Different particle size tablets were crushed in batch and a sieving technique was employed. We were successful in defining and reproducibly (b) (4) spanning the full range of reformulated OxyContin particle sizes achievable :

- Band 1 =
- Band 2 =
- Band 3 =
- Band 4 =
- Band 5 =
- Band 6 =
- Band 7 = core powder containing oxycodone active pharmaceutical ingredient (API) and excipient (used as control)

Study 2: Extraction in Solutions

This study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after small volume extraction in solutions. The goal was to determine and compare the API release kinetics for OxyContin and

reformulated OxyContin using a wide variety of solvents on a range of particle bands (b) (4)

Experiments were performed at (b) (4) and (b) (4)

API release profiles for all strengths and bracketed bands 1, 4 and 6 of

) was not faster than for crushed OxyContin when carried out a (b) (4) the reformulation's API release profile approached that of crushed OxyContin, but was never faster.

. Overall, even the finest particle size bands of reformulated OxyContin did not release oxycodone into solution as rapidly as similarly sized particles of current formulation OxyContin tablets at room temperature.

Study 3: Dissolution in Ethanol

This study was designed to compare the performance of OxyContin and reformulated OxyContin in dissolution experiments conducted with

. The goal was to determine if and characterize how the dissolution profiles for API release differed in (b) (4)

f2 similarity values (50-100 concordant, <50 discordant), calculated from the mean of 6 replicate analyses, for dissolution profiles (all bands of all strengths) in as compared to dissolution profiles in (b) (4). The values for reformulated OxyContin ranged from 29-64, while for OxyContin the values were 96, 67, and 84. For reformulated OxyContin, 12 of the 42 f2 values were within the 50-100. The remaining 30 f2 values were below 50, indicating dissimilarity. Reformulated OxyContin dissolution rates in were slower than those seen in (b) (4) in 28 of these 30 cases. For the remaining two discordant cases, aberrant data points at 10 minute sampling time point likely contributed to skewing of the results. The overall kinetic results show similarity of the results. Overall the API

release kinetics of reformulated OxyContin in (b) (4) solution was similar to those of (b) (4) alone.

Study 4: Extraction in Advanced Solvents

This study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after small volume extraction in (b) (4) The goal was to determine and compare the API release kinetics for OxyContin and reformulated for a range of particle bands.

Three particle size bands (bands 1, 4 and 6) were tested to bracket the full range of sizes by including intact tablets, medium and fine particles.

Intact reformulated tablets maintained controlled-release properties (b) (4) (b) (4) and up to (b) (4) in Smaller particles in the (b) (4) range maintained some controlled-release in (75% API release as compared to >90% release with crushed OxyContin), while both bands 4 and 6 (b) (4) maintain controlled-release up (b) (4). API release for crushed OxyContin reaches (b) (4) . Repeating these experiments at (b) (4) temperatures did not significantly alter the API release rates as compared to experiments performed at (b) (4) for all bands studied. was not an effective extraction solvent for reformulated or crushed current OxyContin at either (b) (4) (The maximum API release seen at any time point was observed with and crushed current OxyContin at which were measured at 29% and 23%, respectively.

Study 5: Syringability, Injectability and Extraction after Vaporization

These experiments were designed to simulate preparation for intentional misuse and abuse via intravenous and inhalation consumption. The goal of these experiments were 1) to determine how much API could be loaded and delivered via a syringe for intravenous abuse 2) to determine how much API was released after vaporization of the product.

The ability to aspirate or inject solutions of reformulated OxyContin powder was dependent on the could not

be aspirated or expelled from a syringe, while (b) (4) were syringable and injectable using an (b) (4). The amount of API that was syringable via an (b) (4) (b) (4) (b) (4) Overall although by using (b) (4) it was feasible to syringe or inject the material, the amount of API recovered was low and the , as compared to similar sample preps for OxyContin. To assess the feasibility of smoking reformulated OxyContin a (b) (4) Simulated smoking of all strengths of reformulated OxyContin resulted in (b) (4) (b) (4) (b) (4) Vaporization of API from reformulated OxyContin was ineffiecient.

Study 6:

Study 7: Complex Extraction with Advanced Solvents Using Liquid Phase Extraction

(b) (4)

[redacted]

[redacted].

Conclusions

Using input from FDA, the Advisory Committee and numerous experts in methods of abuse and extraction of API from pharmaceutical products, Purdue conducted seven *in vitro* studies designed to evaluate the [redacted] of the reformulated tablets under a range of known and anticipated "real world" [redacted] employed inadvertently by patients or well intentioned caregivers or intentionally in the setting of purposeful misuse and abuse.

These experimental results suggest that the reformulated tablets

- were superior (less susceptible to tablet manipulation) to the currently marketed formulation in many dimensions tested
- were not more susceptible to tablet manipulation than current OxyContin under any testing condition

- will be (b) (4)
- will be (b) (4) (b) (4)
- will be (b) (4)
- will yield (b) (4)

Further, despite extensive testing under extreme conditions, no unexpected vulnerabilities relative to current OxyContin were identified.

In conclusion, the strengths of this reformulation relative to marketed OxyContin represent an important incremental improvement against actions (b) (4). This suggests that the reformulated tablets will be safer for patients in the context of inadvertent misuse and potentially less attractive for abuse. These data together with data demonstrating bioequivalence to the current formulation of OxyContin are sufficient to support approval of this reformulated product

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Introduction

This purpose of this document is to brief members the CDER Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee in advance of the September 24, 2009 joint hearing on reformulated OxyContin. This report describes experimental work conducted in support of the March 30, 2009 NDA resubmission for reformulated OxyContin. The scope of this document was defined based upon guidance by FDA on June 2009 for Purdue to focus on presenting *in vitro* data to demonstrating the differences in physicochemical properties between the current and reformulated OxyContin.

The body of work described here (and included in the resubmission of NDA 22-272 to the FDA on March 30, 2009) updates the previous *in vitro* testing work performed by Purdue that was submitted with the original NDA 22-272 on November 29, 2007 and presented at the May 5, 2008 Advisory Committee meeting. Design of these studies was heavily influenced by the input provided from the members of the Advisory Committee, experts we have consulted, as well as recommendations from the FDA in both the October 3, 2008 Complete Response Letter and in a closed meeting on January 21, 2009.

This document is broken into several sections:

- An introduction to frame the context of the work described

- A short section describing the polyethylene oxide inert excipient in reformulated OxyContin
- Seven lengthy scientific sections covering the experimental design, results discussion of *in vitro* studies conducted
- A short section containing supplementary information on data summarizing evidence for bioequivalence, risk mitigation and the contents of the NDA 22-272 resubmission
- Discussion and conclusions, including Purdue's interpretation of results, the limitations of the experimental design and outcomes
- Glossary of terms

Three appendices accompany this document summarizing experts consulted (**Appendix I**), more detailed *in vitro* experimental methodology (**Appendix II**), and an introduction to the *in vitro* studies prepared by one of the experts who helped design and analyze the studies, Dr. Edward Cone (**Appendix III**).

The current formulation of OxyContin is referred to as "OxyContin" and the reformulated version of OxyContin is referred to as "reformulated OxyContin" and "the reformulation" throughout this document.

Developing Reformulated OxyContin

HISTORY OF OXYCONTIN

OxyContin® (oxycodone HCl controlled-release) tablets are a proprietary controlled-release oral formulation containing oxycodone as the active pharmaceutical ingredient (API). FDA approved OxyContin in1995 for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. Despite bringing important benefits to patients, problems with misuse, abuse and diversion of OxyContin began to emerge in the late 1990s, sometimes with fatal consequences to both knowledgeable addicts and recreational abusers. Inadvertent misuse by legitimate patients (medication error) and well intentioned caregivers has also occurred after chewing or crushing OxyContin tablets. The current OxyContin formulation has specific vulnerabilities that allow the product to be converted easily and rapidly (e.g., between two spoons or under a coffee mug) into an essentially immediate-release form that can be ingested via multiple routes.

EARLY DEVELOPMENT OF OXYCONTIN

Purdue evaluated several reformulation strategies for OxyContin to mitigate this problem, including different excipient matrices, novel melt extrusion multi-particulate combinations, direct compression mechanisms and inclusion of non-therapeutic active ingredient (bioavailable or not, sequestered or not). Ultimately we chose to pursue development of a modified-release, single-entity reformulation of OxyContin that bioequivalent

to the current formulation but contains a different inert excipient (b) (4)

REFORMULATED OXYCONTIN'S EXCIPIENT: (b) (4) (b) (4)

Reformulated OxyContin uses cured (b) (4) as a platform to manufacture tablets that retain their intended therapeutic properties while (b) (4). When hydrated, (b) (4) (b) (4)e forms a (b) (4) that retards dissolution of the API from intact, crushed, cut or ground tablets. (b) (4) levels in reformulated OxyContin range from ~108-168 mg per tablet depending on the oxycodone tablet strength (see **Table 0.1**).

Table 0.1 (b) (4) **to API ratios for all strengths of reformulated OxyContin**

Tablet strength (mg API)	**Excipient (mg (b) (4))**	(b) (4)**:API Ratio**
10	138.5 mg	13.9
15	133.5 mg	8.9
20	128.5 mg	6.4
30	118.5 mg	4.0
40	108.5 mg	2.7
60	162.5 mg	2.7
80	167.5 mg	2.1

(b) (4) is included in the FDA inactive ingredient guide for oral controlled release tablets, extended release tablets, sustained release tablets and film coated sustained release tablets. The maximum amounts of (b) (4) content (57.9 mg to 543.9 mg) in products already approved by FDA is greater than those contained in any strength of reformulated OxyContin (see **Table 0.1**).

More specifically, the basic excipient used to reformulate OxyContin is (b) (4)), a high molecular weight, (b) (4), water soluble polymeric resin. The structure of (b) (4) where n is the number of oxyethylene groups. If n is less than approximately 2275, corresponding to a molecular weight of 100,000, then the materials are typically referred to as). The grade of (b) (4) used in all strengths of reformulated OxyContin has an approximate molecular weight o (b) (4).

(b) (4) is a white, free-flowing, hydrophilic powder with a mean molecular weight of (b) (4). It is essentially tasteless, colorless, nonionic, and non-caloric. Although described as water soluble, aqueous mixtures of (b) (4) are better referred to as (b) (4).

[redacted] (b) (4) swells and imparts viscosity to aqueous solutions. These properties make it a suitable polymer for use in hydrophilic matrix controlled release systems and in controlled release tablets which are the basis for OROS push-pull pump and [redacted] (b) (4) technology. It is the ability to impart [redacted] (b) (4) that enables [redacted] (b) (4) to function as the release rate controlling excipient in reformulated OxyContin. This property also causes the [redacted] (b) (4) to [redacted] (b) (4) to any aqueous solvent used to extract oxycodone from the tablets. The physical properties of [redacted] (b) (4) are also what cause the reformulated OxyContin tablets to be difficult to break. [redacted] (b) (4)

[redacted] (b) (4) is well-tolerated and has been used as an excipient in multiple widely used marketed prescription and OTC medications, including but not limited to the medications listed in **Tables 0.2** and **0.3**.

Table 0.2 Currently marketed prescription medications containing [redacted] excipient

Prescription drug	API	Date approved	Indication	Manufacturer
Procardia XL	nifedipine	FDA, September 1989	vasospastic angina	Pfizer
Glucotrol XL	glipizide	FDA, April 1994	type 2 diabetes	Pfizer
DynaCirc CR	isradipine	FDA, June 1994	hypertension	Reliant
Covera HS	verapamil hydrochloride	FDA, February 1996	hypertension and angina	Pfizer
Ditropan XL	oxybutinin chloride	FDA, December 1998	urinary incontinence &	Alza
Concerta	methylphenidate	FDA, August 2000	ADHD	J&J McNeil, Alza
Proquin XR	ciprofloxacin hydrochloride	FDA, May 2005	uncomplicated urinary tract	Depomed
Glumetza ER	metformin hydrochloride	FDA, June 2005	type 2 diabetes	Depomed
Jurnista	hydromorphone hydrochloride	EMEA, August 2006	moderate to severe chronic	J&J - Janssen Cilag, Alza

Table 0.3 Currently marketed over the counter medications containing [redacted] (b) (4) excipient

Product	API	Manufacturer
Pediatric Vicks Formula 44e Cough & Chest Congestion Relief Liquid	dextromethorphan hydrobromide, guaifenesin	Procter & Gamble
Pediatric Vicks Formula 44m Cough & Cold Relief Liquid	chlorpheniramine maleate, dextromethorphan hydrobromide	Procter & Gamble
Sudafed Nasal Decongestant Tablets	pseudoephedrine hydrochloride	McNeil Consumer
Theraflu Thin Strips Daytime Cold & Cough	dextromethorphan hydrobromide, phenylephrine hydrochloride	Novartis Consumer
Theraflu Thin Strips Nighttime Cold & Cough	diphenhydramine hydrochloride, phenylephrine hydrochloride	Novartis Consumer
Vicks Formula 44 Cough Relief Liquid	dextromethorphan hydrobromide	Procter & Gamble
Vicks Formula 44E Cough & Chest Congestion Relief Liquid	dextromethorphan hydrobromide, guaifenesin	Procter & Gamble
Vicks Formula 44M Cough, Cold & Flu Relief Liquid	acetaminophen, chlorpheniramine maleate, dextromethorphan hydrobromide	Procter & Gamble

LATE DEVELOPMENT OF REFORMULATED OXYCONTIN

Purdue submitted an NDA for reformulated OxyContin to FDA on November 29, 2007 (NDA 22-272) and was subsequently the subject of a May 5, 2008 Advisory Committee meeting that considered on proposed labeling in the application. The discussion at this meeting also covered the robustness of the *in vitro* testing presented and Purdue's risk mitigation plans. The Advisory Committee voted against approval of reformulated OxyContin, based on the concerns described below.

Purdue then received an October 3, 2008 Complete Response Letter from FDA requesting additional physicochemical testing of the reformulated tablets. After designing and completing further experimental work to address the concerns raised in the Complete Response Letter, Purdue resubmitted an updated application for NDA 22-272 on March 30, 2009. This resubmission is an application for bioequivalent reformulated OxyContin without any request for label claims regarding the potential benefits of the physicochemical properties of the new formulation against tampering or accidental misuse.

A second FDA Advisory Committee meeting will be held on September 24, 2009 with a specific focus on *in vitro* testing data to assess whether Purdue's resubmitted application is sufficient for approval.

INPUT FROM MAY 5, 2008 ADVISORY COMMITTEE

The May 5, 2008 Advisory Committee raised several important concerns about the *in vitro* data presented at that time (and included in the original NDA 22-272 submission in November 29, 2007). Purdue considered the following concerns articulated by the Advisory Committee carefully in designing the new body *in vitro* studies presented here (and included in the resubmission of NDA 22-272 on March 30, 2009):

- Correlation of the testing to "real world" abuse (particle size and equipment)
- Robustness of testing (limits of testing)
- Completeness of testing (types of tests and number of tablets)
- Quality control of testing (including blinding)
- Third party execution and auditing

INPUT FROM FDA

On January 21, 2009 FDA met with Purdue and agreed that the additional *in vitro* studies of physical and chemical manipulations that are necessary for review or approval must:

- Be designed in consultation with individuals experienced in the intentional extraction of oxycodone from OxyContin for abuse
- Be designed in consultation with experts on extraction techniques to fully assess the testing protocols and

- For the data to be interpreted upon completion by experts
- Evaluate relative rate of release of API from all strengths of crushed and milled tablets in multiple solvents (i.e., confirm that dose dumping does not occur)
- Document how altering the grinding conditions (time, type of grinder) would influence the rates of API release
- Be conducted in a blinded manner, preferably by an independent third party
- Be validated to ensure they are conducted in a reproducible and meaningful manner

INPUT FROM EXPERTS CONSULTED

Purdue also consulted with experts in drug abuse, “tampering approaches”, and analytical pharmaceutics (see **Appendix I**) to design, analyze and interpret the *in vitro* studies described here. These experts provided two important types of input. First, experimental design of each protocol must include the following elements considered necessary to yield reliable scientific data:

- Testing of all dose strengths of reformulated OxyContin
- Testing methods extended to determine failure limits
- Inclusion of adequate controls for comparison to OxyContin
- Sufficient replicates for evaluation of method variability

- Method validation procedures
- Investigation of a range of conditions on outcome of results (e.g., temperature, time)
- Use of independent laboratories
- Testing under blind conditions to the extent possible

Second, the overall body of *in vitro* studies should be designed to simulate the following "tamper" techniques anticipated in the real world:

- Crushability: chewing, cutting, grinding, powdering
- Swallowing: chewed or powder (dissolution)
- Effect of co-consumption of alcohol on "dose dumping"
- Extraction (simple and complex methods)
- Injection (syringability and injectability)
- Nasal insufflation (snorting/sniffing)
- Smoking

Purdue used the above input from FDA, the Advisory Committee and other experts to design the body of *in vitro* studies described below. To date no

"gold standard" approaches have been established for this type of "tamper testing". The intent of the experiments we designed together with experts we consulted (see **Appendix I**) was to test the physical properties of reformulated OxyContin tablets under a wide range of expected "real world" tablet manipulation scenarios. These studies assessed both the strengths and limitations of this reformulation compared to the current formulation when exposed to various means of simple or complex physicochemical manipulations.

In vitro testing of reformulation's physicochemical properties

OVERVIEW OF EXPERIMENTAL STUDIES

Protocols were developed with the above input in mind and in consultation with experts in drug abuse, abuser tampering methods and analytical pharmaceutics (see **Appendix I**) in order to address the concerns raised by FDA in the October 3, 2008 Complete Response Letter. After internal validation of the protocols to ensure reproducibility and consistency across experiments, methods were standardized and transferred to third party vendors. The majority of experiments were performed by two contracted independent third party vendors (Aptuit, Kansas City, MO and Catalent Pharma Solutions, Research Triangle Park, NC). Personnel performing the experiments were blinded to the extent possible. Division of work between these two vendors was capacity-driven, with a goal to complete the experiments as expeditiously as possible. Upon completion of the studies, both independent third party vendors and internal Purdue staff performed extensive quality assurance analysis of the resulting data.

The rationale for the study designs in this report are based on two concepts: A) to experimentally standardize common and uncommon methods of misuse both simple and complex, B) to define the specific strengths of the reformulation, and C) consider the complete API release from the tablet as a final endpoint for all experiments.

The data is presented to provide a clear understanding of the performance of reformulation under simple or complex techniques of tampering that may be encountered in the "real world". The experiments test the reformulation under the following conditions:

- Extraction in small volumes of solvents encompassing ranges of pH, polarity, and temperature
- Dissolution "dose dumping" in ethanol
- Syringability
- Injectability
- Extraction after vaporization (smoking inhalation)
- Advanced cold extraction of API
- Advanced liquid-phase extraction of AP

Dr. Edward Cone, one of the external experts consulted, has written an introduction document (see **Appendix III**) to accompany the complete data package submitted to FDA describing his views on how Purdue's *in vitro* experimental studies represent "real world" scenarios of abuser and misuser manipulations (inadvertent and intentional). Dr. Cone's expertise is in chemistry and pharmacology of drugs of abuse, tablet tampering methods, drug delivery systems, pharmacokinetics, and drug testing methodologies.

To the best of our knowledge these experiments were the first of their kind in terms of scale. These studies were designed with two goals in mind:

- First, to fully characterize the (b) (4) reformulated OxyContin under both common and extreme "real world" abuse and misuse (b) (4) methods
- Second, to compare the performance of OxyContin to that of reformulated OxyContin under all conditions tested

Many of the experiments had to be designed without any significant input from precedent material. Development protocols were created *de novo* to translate known and anticipated "real world" tamper protocols that were identified by consulting with drug abuse experts and studying abusers internet discussion forums on (b) (4) methods (e.g., erowid.org, blulight.ru and others) into systematic and reproducible laboratory procedures. The sequence in which these studies are presented below follow the order in which the experiments were designed and executed order as well as the presentation order of the origina (b) (4) report submitted to FDA with our NDA resubmission on March 30, 2009.

STANDARDIZATION OF PARTICLE SIZES TESTED

Typically the misuse of OxyContin involves manipulating tablets in one of several ways for the purpose of defeating the controlled-release properties (see **Appendix III**). Reducing the tablet to a powder allows immediate access to oxycodone HCl by disrupting diffusion barriers and increasing the surface area of drug particles for more efficient oxycodone extraction. Other

forms of manipulation such as solvent extraction and (b) (4) alteration are often attempted alone or in conjunction with particle size reduction.

Because preparation for misuse and abuse of the reformulation will most likely involve manipulating tablets to reduce particle size, the effect of particle size is tested throughout all manipulation scenarios. When consulting an expert panel (see **Appendix I**) about tools used and methods of preparation for misuse, it became apparent that while some common approaches exist, realistically there is no limit to what will be attempted in the "real world". For this reason, and given that one of the protective properties of the reformulation is increased hardness of the tablet, these "real world" techniques become subjective. In the "real world", the degree of manipulation depends on an individual's strength, determination and available equipment. Time, effort and available equipment are the most impactful variables in designing an *in vitro* study that is intended to simulate what might be attempted in the "real world".

Due to the scope of the seven studies described, continual application of household devices in a laboratory setting became impractical. Additionally analyst to analyst variability and the use of household tools that can not be subjected to calibration and standardization, made it impossible to reproducibly manipulate the tablets using these tools

To standardize this approach, we defined the limits of particle size reduction achievable by subjecting reformulated OxyContin tablets to a myriad of household devices. The upper limit (largest particle size) was generated a slightly indented, intact tablet. The lower limit (smallest particle size) was generated using Other successful "real world" methods) generated particle sizes that fall within these limits. To be sure that the laboratory experiments were standardized and reproducible, was used to create the aforementioned particle size fractions, referred to as *bands* in this report. The particle sizes were divided into ranging from intact tablets to particles smaller than plus a seventh control band

- Band 1 = deformed intact tablet
- Band 2 =
- Band 3 = (b) (4)
- Band 4 = (b) (4)
- Band 5 = (b) (4)
- Band 6 = (b) (4)
- Band 7 = core powder containing API and excipient prior to undergoing manufacturing process (used as control)

These distinct bands represent the full range of particle sizes likely achievable during preparation for misuse, accidental or otherwise, by the general population.

STUDY 1: (b) (4) FRACTIONATION OF TABLETS

Objective

This Study was designed to survey the number of techniques that could be employed to (b) (4) alter OxyContin formulations. The goal of these experiments were to broadly identify and characterize the methods and outputs that could be used for further (b) (4) for the purposes of standardization of experiments.

Design

Techniques that could be employed to (b) (4) reduce reformulated tablets were surveyed. These included simple or complex (b) (4) devices, [redacted] identified and tested for their ability to (b) (4) of the reformulated OxyContin tablets. Following (b) (4) fractionation, (b) (4) used to separate (b) (4) of particles generated. Each (b) (4) device produced a (b) (4) sizes that were either totally discrete or overlapping with particle ranges produced by other devices

A standardized method was developed and tested to reproduce these discrete bands for further testing in Studies 2-7. We further examine whether (b) (4) of tablets with (b) (4) changed the complexity and time required to create (b) (4) sizes. The endpoint for these experiments was to generate and describe the discrete (b) (4) bands that can be produced by multiple (b) (4)l means. Data generated from these experiments include distribution curves for particle sizes generated with tablets at (b) (4) and descriptive observations regarding particle size generation when (b) (4). The complexity and time that was required to create each curve was recorded. Comparator data was generated for OxyContin tablets after similar manipulation. The methodology utiltized in these experiments is described in greater detail in **Appendix II**.

Results

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The time or effort required to reduce the size of reformulated OxyContin tablets into small fragments or particles was dependent (b) (4) used. **Table 1.1** contains this information on devices in order of increasing

Particle sizes obtained with household techniques

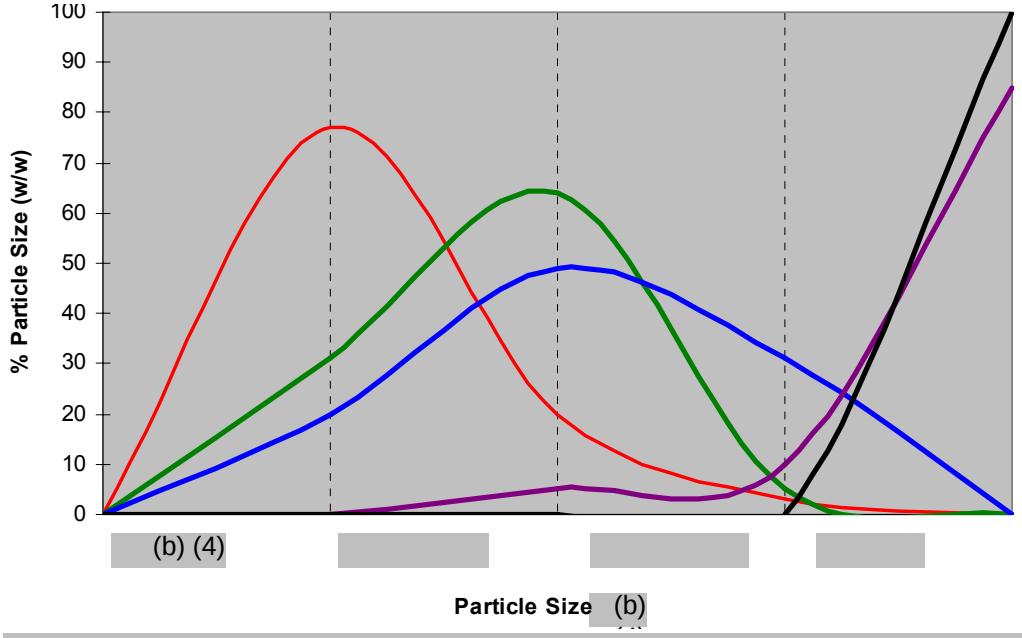
Reformulated OxyContin particle sizes obtained using (b) (4) techniques ranged in size from an (b) (4) produced (b) (4) (b) (4) to (b) (4) (77% of total) when applying a (b) (4) (b) (4) - the most effective technique for (b) (4) fractionating reformulated tablets. This (b) (4) size was achieved by subjecting reformulated tablets to increasing amounts of (b) (4) until no further meaningful reduction in particle size occurs; at (b) (4) (b) (4) (b) (4) Data for end point determination using (b) (4) grinder is found in **Figure 1.1**. All other (b) (4) devices, shown in **Figure 1.2**, resulted in a range of particle sizes that fall within the limits set by the .

To standardize this method, particles were generated r and sieved to produce four discrete bands consisting of the following fractionated (b) (4) (b) (4) Use of a (b) (4) resulted in the most reproducible and efficient approach for the recovery of particles. We observed that an API loss upwards of 10-16% occurred when using the as opposed to 3% loss

when using [redacted]. The maximum API released of bands 5 or 6 do not generally reach 100% as a result of this preferential API loss.

Figure 1.1 Reformulated OxyContin – particle size results for household devices

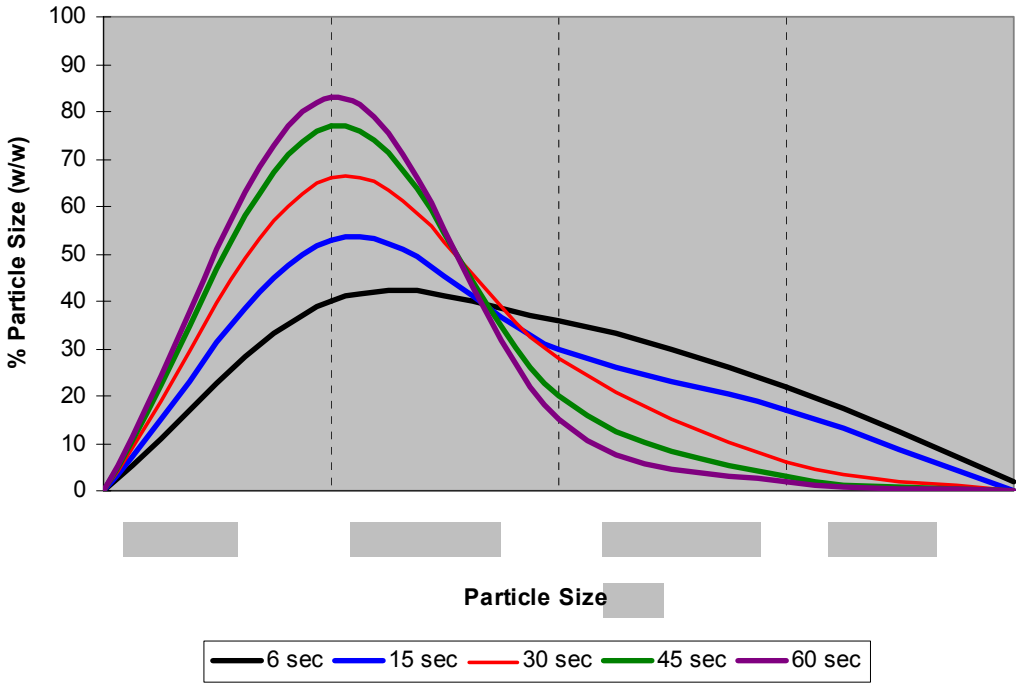
NOTE: For illustrative purposes the figure contains smoothed curves generated from values for % weight retained (y-axis) on a series of sieves (x-axis)



[redacted]

Figure 1.2 Milling results grinder

NOTE: For illustrative purposes the figure contains smoothed curves generated from values for % weight retained (y-axis) on a series of sieves (x-axis)



As defined in this scheme, band 1 is an (b) (4) tablet, with sligh (b) (4) (b) (4) that is caused by (b) (4) Band 7 is the finest powdered material, with 100% (b) (4). This is the (b) (4) for reformulated OxyContin. This powder consists o (b) (4) that is (b) (4) to form the reformulated OxyContin tablets. This band was used as a “positive control” in some experiments, demonstrate that API release was not dependent on any forms of mechical manipulation. This (b) (4) powder, band 7, is not available to misusers and abusers as it is an (b) (4) solely used during the (b) (4) process.

In contrast to the other bands, band 3 was obtained by grating tablets on a no sieving step was involved in producing band 3. This approach was conceived to consider all potential particle sizes and shapes that may be available for further analysis. Analysis of samples from this band with microscopy demonstrated that the particle sizes achieved with the ranged between in width with a variety of long and short lengths. Because of these different (b) (4) dimensional properties, direct comparison of this band with the other bands may not result in a linear correlation for the extraction data.

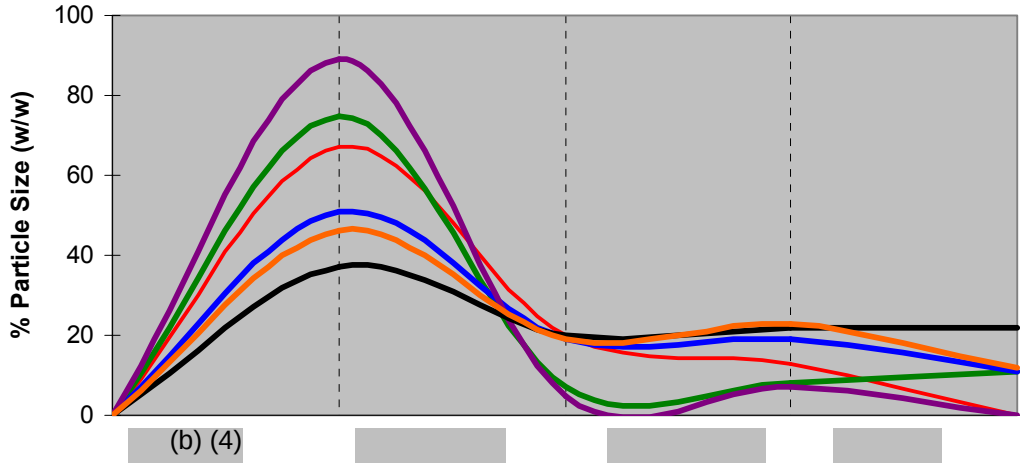
used to render current OxyContin a powder; the resulting particle size was 92% (b) (4) and was

achieved within (b) (4). Many of the other (b) (4) devices that were used were also effective in easily crushing OxyContin into powder form, including simple and readily available items such as . **Figure 1.3** summarizes the relationship between (b) (4) devices and particle size reduction for OxyContin.

The premise for this strategy to standardize the particle sizes that are to be tested was that the dissolution and extraction behavior of any of the seven discrete particle size bands defined above using a and sieve can be related to the same characteristics of particles that are generated by physical manipulation using (b) (4) equipment. In other words, any (b) (4) or "real world" device would result in a range of particle sizes that can be characterized by a set of kinetic API release curves. To standardize the experiments and to be able to perform them blindly via a third party, it was not practical or precise to use (b) (4) devices for future extraction methods. Therefore by showing that the (b) (4) could be standardized into (b) (4)r particle bands, we were able to standardize and industrialize all the experiments.

Figure 1.3 OxyContin – Particle sizes resulting from experiments with (b) (4) tools

NOTE: For illustrative purposes the figure contains smoothed curves generated from values for % weight retained (y-axis) on a series of sieves (x-axis)



(b) (4)

(b) (4)

To be sure that the reformulated tablet was not preferentially vulnerable to easy crushing after (b) (4) were evaluated. Observations for each of the conditions are found in **Table 1.3**. (b) (4) of tablets was found to slightly increase the ease with which the tablets could be crushed using (b) (4) not outside of the range of particles achieved at room temperature. (b) (4) the tablets did not improve the ability to create powder from the reformulated OxyContin tablets.

Table 1.3 Effect of [redacted] pretreatment on the subsequent effectiveness of [redacted] tools in [redacted] reformulated OxyContin to [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	
	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Discussion

Many commercially available [redacted] (b) (4) tools were unable to successfully reduce the particle size of the reformulated OxyContin tablets. Although hard, the tablets are malleable and do not shatter as a nut or a peppercorn

would when subjected to some of these devices. In addition, because the [redacted] properties of the reformulation is based on its [redacted], the characteristics of API release from the tablets, either as intact or in particles, differs significantly from that of crushed OxyContin powder. These [redacted] properties are expected to retard the release kinetics of API from the reformulation (even when crushed into [redacted] particles or tablet [redacted]) and to make it significantly more difficult to syringe, inject or smoke the material.

Reformulated OxyContin tablets were resistant to crushing and particle size reduction using readily available [redacted] devices. Of the [redacted] devices employed in this Study [redacted] the particle size of reformulated tablets. In contrast, the current formulation of OxyContin was quickly and easily rendered a fine powder using tools as simple as two spoons. Increasing amounts of time or effort were required to achieve progressively [redacted] (b) (4) particle sizes of the reformulated tablets (in contrast with the binary response, intact or crushed condition, observed with the current OxyContin formulation). See **Figure 1.2** and **Figure 1.3**. The reproducible banding of particle sizes was only possible after evaluating the full range of achievable particle sizes using a wide variety of [redacted] tools. This banding strategy is an effective means of standardizing experiments that may be otherwise subject to variability due to the inherent subjective nature o [redacted] (b) (4) tablets with [redacted] (b) (4) tools. The six particle size bands defined here were used throughout Studies 2-7.

STUDY 2: EXTRACTION IN [redacted] (b) (4) [redacted] (b) (4) SOLUTIONS

Objective

This Study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after [redacted] (b) (4) extraction in [redacted] (b) (4) solutions. The goal was to determine and compare the API release kinetics for OxyContin and reformulated OxyContin using a wide variety of solvents on a range of particle bands.

Design

Study 2 was comprised of series of simple extraction protocols designed to cover a range of known and predicted methods of tampering with reformulated OxyContin. Simple extraction methods are generally employed for injection. The first step in such a process requires crushing a tablet followed by [redacted] (b) (4) extraction in a suitable [redacted] (b) (4) [redacted]

Simple extraction protocols were developed to assess the difficulty of extraction, with the intent of producing a solution that could be injected or ingested via other routes of administration.

Extraction experiments were performed for all tablet strengths covering all ranges of particle size bands. Because higher temperatures facilitate faster extraction kinetics in general, all extractions were performed both a (b) (4) (b) (4) (b) (4) and at an elevated temperature

Multiple time points were sampled to generate a kinetic representation of API release. Data from these experiments include band-specific kinetic curves describing the release profile of API over time from all bands in multiple solvents at room temperature versus elevated temperature. It is important to re-emphasize that the endpoints for all of these experiments were defined as the time to complete release of API from the sample regardless of whether this was reformulated or current OxyContin.

Details of protocol development and experimental methodology are provided in **Appendix II**. The statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results are separated by solvent type and presented below.

Results

(b) (4)

(b) (4)

.

(b) (4)

(b) (4), the release of API from different particle sizes of reformulated OxyContin was graded in proportion to the size of particles tested. The kinetic results should be contrasted with those

for crushed OxyContin which demonstrate a binary, immediate release profile. (b) (4) [redacted].

[redacted]

(b) (4)

(percent of label claim API extracted)

It was expected that solutions at higher temperatures would lead to faster release of API than the same solutions at room temperature. (b) (4) (b) (4) (b) (4) (b) (4). Under these conditions, band 1, at all dosages tested, maintains its controlled-release property (b) (4). This API release rate was significantly slower than the release rate of (b) (4) (b) (4) and that seen with crushed OxyContin (b) (4) (b) (4) properties of reformulated OxyContin, (b) (4) (b) (4)

API release from band 2 (b) (4) was (b) (4) faster than that for band 1 but substantially slower than all other bands including crushed OxyContin (b) (4) (b) (4)). Bands 2 and 6 did not reach the API release plateau (b) (4). No difference in the API release rate was observed between bands 3-5 of reformulated or crushed OxyContin. The curves reached a plateau, maximum API release, (b) (4).

Band 1 maintains its controlled-release properties (b) (4) when extracted (b) (4), (b) (4) (b) (4) (b) (4) To be sure that these conditions did not signify new vulnerabilities for reformulated OxyContin in contrast to (b) (4) current OxyContin, the same extractions were performed a (b) (4)

OxyContin across all strengths. [redacted] The figure shows that API release profile for [redacted] OxyContin is significantly faster than that for [redacted] t reformulated OxyContin, band 1, [redacted] (b) [redacted]). At [redacted] kinetics from band 1 reaches a plateau [redacted] while intact OxyContin reaches its plateau [redacted]. As shown in these figures, although [redacted] reformulated OxyContin (band 1) releases API faster at [redacted] when compared to API release [redacted] the release is slower than what is seen with [redacted] OxyContin extracted under the same conditions [redacted] Therefore despite earlier release of API by [redacted] reformulated OxyContin under these conditions, the reformulation is not vulnerable when compared to OxyContin.

(b) (4) ***solvents***

Figure 2.4 presents data for bands 1, 4, 6 of reformulated OxyContin and crushed OxyContin in (b) (4) extractions with (b) (4) (b) (4) he data was collected at 10 minutes, 60 minutes and 18 hours, in contrast to (b) (4) extractions (b) (4), only bands 1, 4 and 6 were tested for (b) (4) (b) (4) (b) (4) (b) (4)

Full kinetic API release data for extraction with (b) (4) are presented in **Figure 2.4 (top panels).** For both of these solvents band 1), band 4 (b) (4) and band 6) maintain controlled-release properties (b) (4), (b) (4) (b) (4); in (b) (4) band 1,4 and 6 release (b) (4) all at (b) (4) (b) (4). These results should be compared to those for crushed OxyContin which releases >90% API by (b) (4). In comparing (b) (4) (b) (4) as solvents, more API was released from band 1 (b) (4) (b) (4) (b) (4) suggesting that (b) (4) may be a slightly better solvent than (b) (4) (b) (4) and better solubility for API release from the matrix (b) (4)

Figure 2.4 Reformulated OxyContin extraction in (b) (4) **solvents at** (b) (4) (percent of label claim API extracted)

(b) (4)

e
s)

0
e
s)

The above experiments ([redacted] were performed at room temperature and duplicated in a [redacted] to examine how rates of API release could be affected by elevated temperatures. Even under [redacted] (b) (4) at [redacted] (b) (4) [redacted] reformulated OxyContin (band 1) maintained some control release property [redacted] (b) (4) at all strengths tested [redacted] (b) (4) for [redacted] (b) (4) respectively, data not shown). [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) in the API release rate was observed between bands 4 and 6 of reformulated and crushed current OxyContin. API release of about [redacted] (b) (4) was reached as early as [redacted] (b) (4). One [redacted] (b) (4) where [redacted] (b) (4) [redacted] (b) (4) (data not shown).

In these set of experiments, while band 1 maintained its controlled-release properties [redacted] (b) (4) when extracted with [redacted] at 25 °C, the API release profile for band 1 extracted in the same solutions at [redacted] was [redacted] (b) (4). To be sure that these conditions did not signify new vulnerabilities for [redacted] (b) (4) reformulated OxyContin compared to [redacted] (b) (4) current OxyContin, the same extractions were performed a [redacted] for [redacted] (b) (4) OxyContin. Under these conditions, only 10, 40 and 80 mg strengths [redacted] (b) (4) OxyContin were tested. As previously noted, the selected strengths adequately represent the full spectrum of all six strengths of OxyContin. [redacted] (b) (4) OxyContin released API significantly faster than [redacted] (b) (4) reformulated OxyContin, band 1, in [redacted] (b) (4) [redacted] (b) (4)

from intact OxyContin (b) (4) (b) (4) from intact OxyContin) (Data not shown). Therefore despite the fact that API is released earlier under these conditions, the reformulation is not more vulnerable than OxyContin.

Full kinetic API release data for extraction with at are represented in **Figure 2.4 (middle panels).** Both extracted API from crushed OxyContin (90% API released (b) (4) (b) (4). For reformulated OxyContin, this release rate was band-specific. As shown in **Figure 2.4**, the API release profiles of (b) (4) reformulated OxyContin (band 1) were similar, maintaining a controlled-release profile up to the end point ((b) (4) (b) (4)). For band 4 (b) (4) API release rates in were similar (b) (4) (b) (4) However, more API was released at (b) (4) hours than (b) (4)). For band 6 (b) (4) the (b) (4), some control was retained (b) (4) in but (b) (4) of API was released at (b) (4) in (b) (4) data suggest that a slightly better solvent than for (b) (4) r particles.

Elevated temperature extraction experiments for (b) (4) solutions were performed a . At this temperature only bands 1 and 4 showed controlled-release properties in both

, and . Band 6 had some control in API release in but not in . Greater than API was released .

was a poor solvent for extracting API from crushed reformulated or current OxyContin (**Figure 2.4, bottom panel**). Increasing the length of time or temperature for extraction by did not render it a better solvent. Maximum API extracted at any time point from was from band 6 and crushed OxyContin at abou .

(b) (4) ***solutions***

Multiple bands for all dosages of the reformulation were evaluated in extraction via (b) (4). Bands 1 (b) (4)), 4 and 6 (b) (4)) were used because these bands effectively bracket (b) (4) reformulation tablets. Kinetic API release data for (b) (4) solutions a are represented in **Figure 2.5**. Bands 1, 4 and 6 of reformulated OxyContin are extracted with (b) (4) solutions and data collected at minutes, (b) (4)

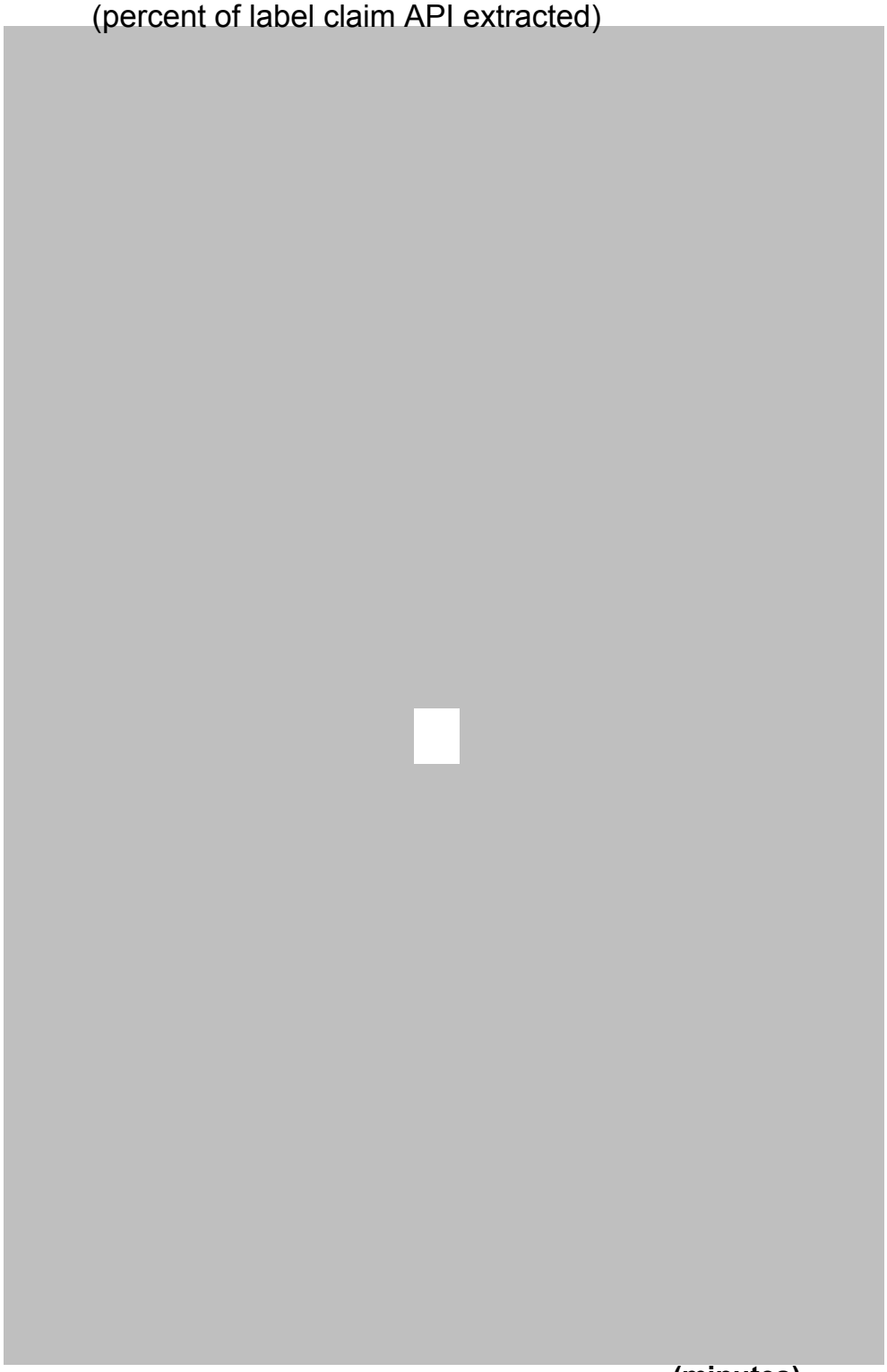
Figure 2.5 Extraction of reformulated OxyContin in (b) (4) at (b) (4)

(percent of label claim API extracted)

Figure 2.5 (continued)

Extraction of reformulated OxyContin in (b) (4) **at** (b) (4)

(percent of label claim API extracted)



(minutes)

API release profiles are similar in (b) (4). API release profiles in (b) (4) was significantly slower than those seen in (b) (4).

(b) (4) reformulated OxyContin (b) (4)) maintained its controlled-release properties throughout the time points. Band 4 ((b) (4) and band 6 (b) (4) releases (b) (4) than band 1, but maintains some of the controlled-release properties (b) (4). . As the a reformulated OxyContin tablet is (b) (4) g, the rate of API release (b) (4)i.e., smaller particles release API faster than larger ones. Despite this acceleration, smaller particles maintain some controlled-release properties (b) (4). Even the smallest particles release API slower than crushed OxyContin (b) (4) time point.

Extractions were duplicated for the above (b) (4) experiments to examine how rates of API release were affected. (b) (4) reformulated OxyContin (band 1), at all strengths tested, maintained some of its controlled-release properties (b) (4) for al (b) (4) tested.

Once the [redacted] (b) (4) [redacted] (b) (4) in the API release rates between bands 4 and 6 of reformulated or current OxyContin tablets was observed. Maximum API release plateau was reached [redacted] (b) (4) [redacted] Even [redacted] buffer was less effective in extracting API from reformulated OxyContin.

To be sure that these conditions did not signify new vulnerabilities for intact reformulated OxyContin compared to [redacted] (b) (4) t current OxyContin, the same extractions were performed at [redacted] (b) (4) (10, 40 and 80 mg strengths). [redacted] (b) (4) [redacted] (b) (4) OxyContin releases API significantly faster than [redacted] (b) (4) reformulated OxyContin (band 1) extracted at [redacted] (b) (4) Therefore despite the fact that the baseline of API release for [redacted] (b) (4) reformulated OxyContin is shifted a [redacted] the reformulated OxyContin is not more vulnerable than OxyContin.

Discussion

[redacted] (b) (4)

API release rate in [redacted] (b) (4) is a function of reformulated OxyContin particle size. At room temperature, the rate at which API was released is proportional to particle size [redacted] (b) (4) The [redacted] (b) (4) principle predicts that the release properties of reformulated OxyContin, even in smaller particle sizes, may be substantially different than those of crushed OxyContin which does not possess a similar physicochemical character. This [redacted] (b) (4) was demonstrated with [redacted] (b) (4) extraction of band 7, where

the uncured core powder retains some controlled release properties despite the fine particle size of the material. Furthermore because of this the API release characteristics would be expected to correspond to the size of the particles in a graded fashion. The data shown in these experiments support this view. In contrast, current formulation OxyContin appears to show binary API release kinetics in water (performs either as a controlled-release or like an immediate-release formulation). This API release property for OxyContin is independent of the manipulation methods that may be used to reduce its particle size. For OxyContin once the tablet is no longer whole, the release kinetics are binary. This contrasts with the reformulated OxyContin that shows more graded release characteristics.

The controlled-release properties of reformulated OxyContin were reduced y with smaller particle sizes and in This was expected since the increased surface area of smaller particles leads to a greater exposure area for to solvent access and with less protection from (b) (4) and increased physicochemical degradation (b) (4) in similarly reduce the controlled-release properties of reformulation particles.

In conclusion, API release kinetics of reformulated OxyContin extraction appears to be a graded response in proportion to particle size as compared to OxyContin that shows a binary response. Even the smallest particle sizes of reformulated OxyContin l, thereby retaining some of their controlled-release properties when extracted

(b) (4) is a more efficient means of extracting API than (b) (4) extraction (b) (4). Under no condition tested was API release faster from the reformulation than from current OxyContin.

(b) (4) solvents may be used to extract API from reformulated OxyContin. A combination of properties unique to (b) (4) may potentially allow these solvents to extract API more effectively than (b) (4). A number of different OxyContin. API release in (b) (4) was a function of reformulated tablet particle size and the nature of the solvent. Similar to the case with (b) (4), at room temperature the rate at which API was released was proportional to the particle sizes of the manipulated drug product. In contrast, similar to its performance in water, current OxyContin appears to have binary API release kinetics in (b) (4). Regardless of the methods attempted for (b) (4) reduction, OxyContin was reduced to the same particle ranges that behave similarly in releasing API, showing immediate-release kinetics. Reformulated OxyContin, however, shows more graded release characteristics due to the (b) (4) properties of (b) (4)

The controlled-release properties of reformulated OxyContin were reduced (b) (4) with smaller particle sizes in This was expected because the increased surface area of smaller particles lead to greater exposure to solvent with less protection from the (b) (4)

properties of (b) (4). The API release profiles in and at (b) (4) up to (b) (4) were similar. At was slightly better than for extracting API from smaller particles. was a poor solvent for reformulated OxyContin. Neither time nor temperature improved the poor extracting properties of

(b) (4) ***solutions***

(b) (4) solutions with varying pH are also used to extract API from reformulated OxyContin. (b) (4) o (b) (4) may potentially allow these solvents to extract API more effectively than (b) (4). A range o (b) (4) were used to extract API from reformulated OxyContin. API release in solutions was a function of reformulated OxyContin particle size and the aqueous nature and the (b) (4) of the solvent. At (b) (4), the rate at which API was released is proportional to (b) (4) of drug particles. As was the case for (b) (4) and (b) (4) (b) (4), OxyContin appears to show a binary API release kinetics in (b) (4) (b) (4). Regardless of the manipulation methods attempted, OxyContin was reduced to powder fairly easily. Crushed OxyContin particles, regardless of the method of (b) (4)r, behave with immediate-release kinetics. Reformulated OxyContin again shows more graded release characteristics.

The controlled-release properties of reformulated OxyContin are (b) (4) substantially with (b) (4) particle sizes and in (b) (4) solutions. This was expected since the increased surface area of (b) (4) particles

lead to greater exposure to solvent with less protection from the

4

STUDY 3: DISSOLUTION IN ETHANOL

Objective

This study was designed to compare the performance of OxyContin and reformulated OxyContin in dissolution experiments conducted with (b) (4)) mixture of ethanol and (b) (4) (b) (4) (b) (4). The goal was to determine if and characterize how the dissolution profiles for API release differed in (b) (4) versus ethano (b) (4)

Design

Dissolution experiments are performed in standard (b) (4) o (b) (4) or ethano (b) (4) (a v/v mixture of ethanol and (b) (4). All bands from all strengths of reformulated OxyContin were tested and multiple time points were sampled to generate a

kinetic representation of API release. Sampling was continued until no further API release was observed. Data from this experiment include a time series representation of the amount of API released.

Details of protocol development and experimental methodology are provided in **Appendix II**. The statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results

Table 3.1 presents f2 similarity values, calculated from the mean of 6 replicate analyses, for dissolution profiles (all bands of all strengths) in as compared to dissolution profiles (b) (4). The values for reformulated OxyContin range from 29-64, while for OxyContin the values are 96, 67, and 84. Dissolution profiles with f2 values between 50 and 100 are considered similar while values below 50, suggesting discordance between the profiles. In the case of reformulated OxyContin, 12 of the 42 f2 values were within the 50-100 range indicating similarity between results of dissolution in (b) (4) vs. ethano (b) (4). The remaining 30 f2 values are below 50, indicating dissimilarity. Reformulated OxyContin dissolution rates in ethano (b) (4) are slower than those seen in (b) (4) alone in 28 of these 30 cases. This suggests that media containing ethanol has some retarding effect on the rate of oxycodone HCl API release from reformulated OxyContin.

In two instances where the f2 value is below 50, further analysis reveals that the dissolution rate of reformulated OxyContin is faster in ethano compared to alone. These values are presented and highlighted with red shading in **Table 3.1**. The full dissolution profiles for both of these experimental conditions (band 6 from 10 and 15 mg tablets of reformulated OxyContin) are presented in **Figure 3.1**. In both conditions, the dissolution profile in and ethano converge after the point. For the 10 mg sample there was wide variability in the data scatter at the earlier time points. This was most likely due to sampling errors associated with sampling of the finely powdered material. One of the replicates is censored because it was measured at an impossible value of 275% API release. In the 15 mg sample (**Figure 3.1**) one replicate at the the 10 minute time point was also abnormally high (134%). The f2 value is heavily biased by this data point, but to preserve the integrity of the data this value was not discarded.

The remaining time points in the 15 mg profile show consistency with the corresponding SGF data. Slower release rates in ethano are observed in all earlier time points. The dissolution rates of reformulated OxyContin band particles in ethano as compared to are consistently slower or the same.

For illustrative purposes manipulated OxyContin tablets (powdered 10, 40, 80 mg tablets) were evaluated under similar conditions. The data is presented as “OxyContin control” in **Table 3.1**. The dissolution profiles for manipulated OxyContin are similar as indicated by their f2 value (>50

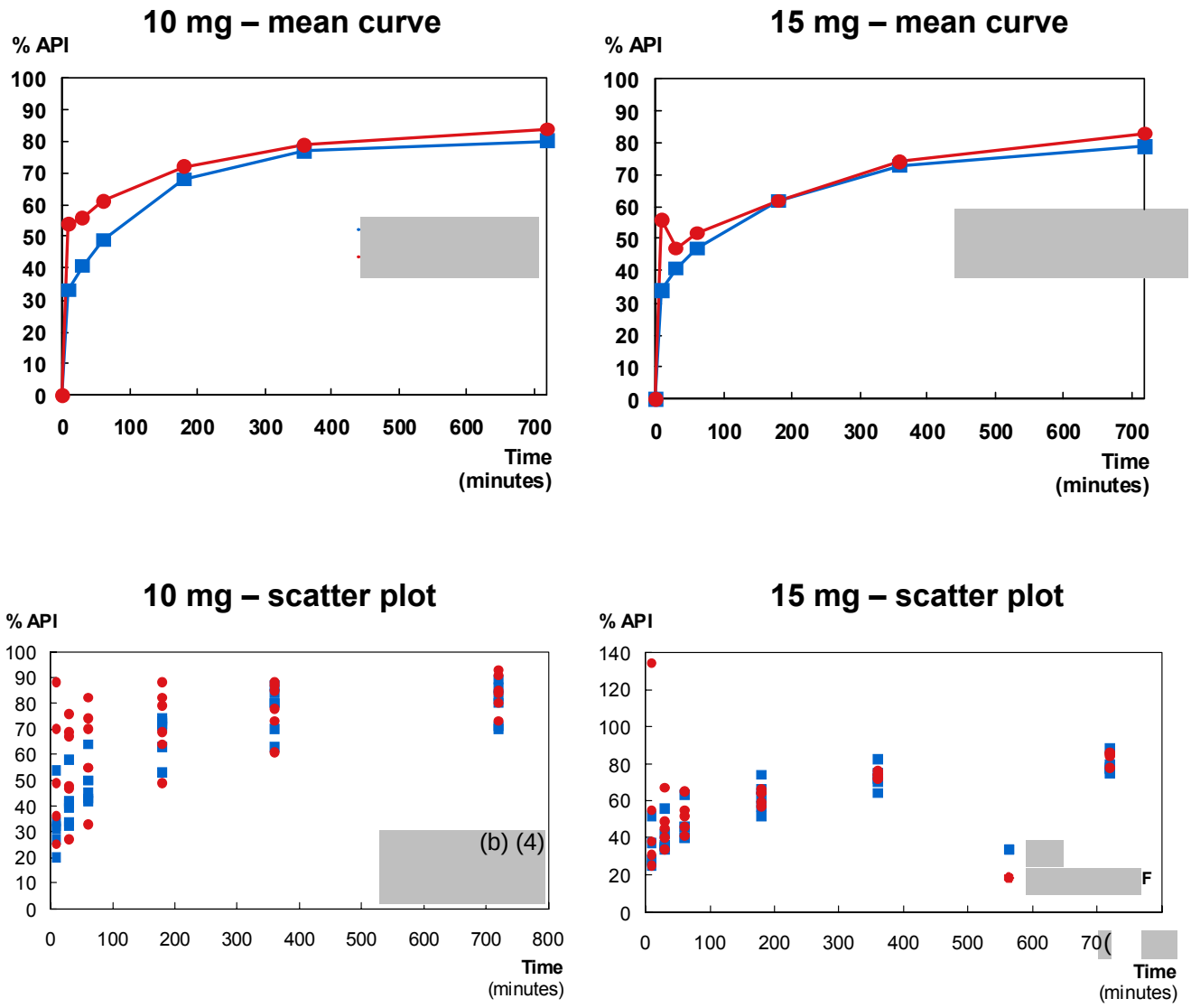
indicates similarity). The dissolution kinetic profiles for OxyContin approach that of an immediate-release formulation in both (b) (4) and (b) (4) (not presented).

The goal of these experiments were to evaluate the properties of reformulated OxyContin in ethanol media and compare that to its profile in (b) (4), the control media. **Table 3.1** shows that intact reformulated OxyContin is not vulnerable to "dose dumping" in ethano (b) (4) F and the baseline kinetics in (b) (4) versus ethano (b) (4) F are identical (data not shown). Similarly powdered OxyContin is not vulnerable to "dose dumping". In the absence of these findings because the baseline relationship for reformulated OxyContin relative to OxyContin was previously established, additional ethanol dissolution analysis for intact OxyContin were not performed.

Table 3.1 f2 Values for 100% [redacted] versus [redacted] ethano [redacted] dissolution results

Sample Strength	Bands							
	Band 1	**Band 2**	**Band 3**	**Band 4**	**Band 5**	**Band 6**	**Band 7 (Uncured core)**	**OxyContin Control**
10 mg	**52**	37	**57**	**54**	**55**	**45**		**96**
15 mg	45	41	38	**53**	49	**48**		
20 mg	46	36	47	**51**	35	**64**	N/A	N/A
30 mg	44	37	48	43	42	42		
40 mg	42	**53**	**61**	**60**	**52**	**51**		**67**
60 mg	47	40	44	48	31	37		N/A
80 mg	47	52	40	43	29	47	29	**84**

Figure 3.1 Reformulated OxyContin (10 and 15 mg) dissolution in SGF versus [redacted] ethanol in [redacted], band 6 particles
(percent of label claim API extracted)



Discussion

Reformulated OxyContin is not vulnerable to ethanol-induced acceleration of API release in dissolution experiments. This observation holds true regardless of particle size as supported by data shown in **Table 3.1**. [redacted], the primary endpoints of these experiments were to examine "dose dumping" by ethanol. We have previously demonstrated that band particles from reformulated OxyContin do not show unusual or accelerated API release properties in [redacted] solutions (see Study 2, [redacted] (b) (4) solvents). Therefore we have concluded that the reformulated product, either [redacted] (b) (4) t or [redacted] (b) (4) particle sizes, is not susceptible to ethanol induced accelerated release either in dissolution studies or in [redacted] (b) (4) extractions.

STUDY 4: EXTRACTION IN ADVANCED SOLVENTS

Objective

This study was designed to evaluate the oxycodone API release characteristics of reformulated OxyContin after (b) (4) extraction in "advanced solvents"--- solvents that are not (b) (4)]. The goal was to determine and compare the API release kinetics for OxyContin and reformulated OxyContin in "advanced solvents" for a range of particle bands.

Design

A simple extraction protocol was developed to assess the efficiency of extraction with organic solvents that are (b) (4). Solvents were selected by polarity and solubility criteria and to adequately cover the range of possible outcomes. Three particle bands representing (b) (4) and (b) (4) were selected to bracket the full range of particle sizes. Extractions were performed at different times to provide a kinetic representation of API recovery. Finally, the experiments in this study were performed both a (b) (4) and understand how temperature influences API release characteristics in these solvents.

Data from these experiments include band-specific recovery curves generated with multiple solvents over time at either (b) (4) or

Comparator data was generated from crushed OxyContin tablets in identical extraction conditions.

Details of protocol development and experimental methodology are provided in **Appendix II**. The statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results

Advanced, non-consumable solutions may be used to extract API from reformulated OxyContin tablets. Kinetic API release data for extraction in [redacted] and [redacted] at (b) (4) are presented in **Figure 4.1 A-B**.

Band 1 [redacted] reformulated tablets) maintains controlled-release properties up to [redacted] in [redacted] and up to (b) (4) in [redacted] Band 4 [redacted] (b) (4) maintained some controlled-release in [redacted] a (b) (4) (b) (4) (76% API release as compared to 98% release with crushed OxyContin), while both bands 4 and 6 (b) (4) maintain controlled-release [redacted] up to (b) (4). API release for crushed OxyContin reaches >90% at (b) (4) in both [redacted] and [redacted]

It is expected that solutions at (b) (4) temperatures would lead to faster release of API than similar solutions at (b) (4) temperature. To test this hypothesis, the above experiments were repeated in a [redacted] with continuous agitation. API release rates [redacted] and [redacted] at [redacted]

were similar to the API release a (b) (4) temperature for all bands studied (data not shown).

was not an effective extraction solvent for reformulated or crushed current OxyContin at either (b) (4) (**Figure 4.1 C**) or was observed with band 6 of reformulated and crushed current OxyContin at (b) (4) which were measured at 29% and 23%, respectively.

Discussion

Band 1 (b) (4) reformulated OxyContin) maintains its controlled release property up to (b) (4) in and up to (b) (4) in The controlled-release properties of reformulated OxyContin is maintained for the smallest particles (b) (4) even up to (b) (4). Smaller particles behave as immediate-release products when extracted in The slower API release rate observed in for all ranges of the particles studied at (b) (4) temperature may be due to the aqueous properties of this solvent. aqueous component of is likely to induce (b) (4) constituent in reformulated OxyContin. This (b) (4) would be expected to retard the release of API.

In contrast to the reformulated product, OxyContin appears to have a binary API release kinetics. API release for crushed OxyContin reaches >90% at (b) (4) in both The API release profile of (b) (4) reformulated OxyContin in is slightly faster at (b) (4) as compared to extraction in water. All other extraction conditions in advanced solvents are slower than corresponding extraction in (b) (4)

Comparison across all solvents tested (Studies 2 and 4)

The aim of Studies 2 and 4 was to better understand the strengths and limitations of reformulated OxyContin tablets in manipulation scenarios designed to extract API in a variety of solvents. Once the extraction studies were concluded the performance of each solvent was compared to the others tested.

STUDY 5: SYRINGABILITY, INJECTABILITY AND EXTRACTION AFTER VAPORIZATION

Objective

These experiments were designed to simulate preparation for intentional misuse and abuse via intravenous and inhalation consumption. The goal of these experiments were 1) to determine how much API could be loaded and delivered via a syringe for intravenous abuse 2) to determine how much API is released after vaporization of the product.

Design

Intravenous use was studied in standard fashion by analyzing the rheological limits of reformulated OxyContin when aspirated into an empty syringe (syringability) and when expunged from a loaded syringe (injectability). To determine the limits of syringability and injectability, the experiments were performed after mixing a fixed volume of (b) (4) er with a (b) (4) (b) (4)) of reformulated OxyContin (b) (4) (b) (4) in these experiments because it represents the (b) (4) condition of reformulated OxyContin. Studies were conducted at both room temperature and after boiling and both syringability and injectability were assessed using a range of needle gauges.

(

An inhalation assay was designed to examine the release characteristics of API from reformulated OxyContin as a proxy for its potential to be smoked. API containing powder was dry heated to vaporization. Vaporized API was extracted with methodology (b and heating tube apparatus. This apparatus uses standard (b to trap the vapors generated after heating and evaporating fine reformulated OxyContin .

Syringability

To determine the syringability of OxyContin were added to of reformulated OxyContin particles and the amount of API successfully aspirated into the syringe was measured. Syringability was assessed using a range of needle gauges. Because heat can alter the rheological properties of some solutions, syringability was assessed both at room temperature and after boiling. To ensure adequate API extraction prior to syringe aspiration, varying amounts of time were allowed after mixing reformulated OxyContin powder . Data obtained from this experiment include the total amount of oxycodone API and the volume that was successfully syringed. Comparator data were generated from manipulated OxyContin tablets.

Injectability

Injectability was assessed by expelling solutions of reformulated OxyContin from preloaded syringes through different gauge needles. The total volume and amount of API expelled was measured for a total

continuous effort to inject. This time point was set with input by experts and is believed to reflect a serious effort by a motivated abuser. To determine the limits of injectability, these experiments were repeated with increasing volumes of (b) (4). To determine how heating the admixture could improve injectability, the experiments were conducted at room temperature and after heating to boiling. The endpoint in these experiments was to define the total amount of API and volume that could be injected from a preloaded syringe. Data from these injectability experiments include the total amount oxycodone API and the volume that is successfully extruded. Comparator data was generated from manipulated OxyContin tablets.

Extraction after vaporization

Inhalation (smoking) was simulated with (b)) and heating tube apparatus. This apparatus uses standard (b) (4)- (b) technology to trap vapors generated after dry heating and vaporizing finely powdered reformulated OxyContin tablets. Upon completion of the experiment the (b) was removed and solvent was used to extract and to recover the total amount of trapped API. The endpoint in these experiments were vapor collection over (b) (4) to ensure that all oxycodone API was either collected or pyrolyzed. Comparator data were generated from both manipulated OxyContin tablets

Methodology for syringability, injectability and “smoking” assays were developed at Purdue. Details of protocol development and experimental methodologies for all of these studies are provided in **Appendix II**. The

statistical approach to calculating the number of samples used in each experiment as well the methodology applied to determine the significance of the results are provided in **Appendix II**.

Results

Syringability

Figure 5.1 contains mean results for each of the syringability experiments. Boxes shaded green indicate the conditions in which aspiration was unsuccessful (i.e., < 1 ml of the sample was aspirated due to viscosity). Yellow and red shaded boxes contain the amount of API (mg) extracted and the volume (ml) aspirated. Color coding was determined by the concentration of the aspirate in mg/ml, which was set as a standard based on the amount of API available in one ml when using a common insulin syringe (a realistic amount based on the type of needle and syringe most widely available to abusers). Results for 10 mg OxyContin tablets were not included due to the low strength and consequent low yield of API. Aspirates obtained for (b) (4) preparations of OxyContin 40 and 80 mg tablets contained (b) (4) The lower concentration limit (b) (4) was used as a cut off in color coding **Figure 5.1**. Yellow indicates that aspiration was successful (>1ml); however, the concentration of the aspirate was (b) (4). Red indicates successful aspiration of a liquid with concentration o (b) (4). As shown in **Figure 5.1** there are (b) (4) conditions (b) (4) temperature and (b) (4) conditions after (b) (4), for reformulated OxyContin, in which the aspirate contains equal and more than (b) (4) None resulted with a 27 gauge needle. In the remaining 135 conditions, the sample could not be aspirated or the concentration of the aspirate was (b) (4) (green boxes).

In contrast, for OxyContin 40 mg and 80 mg tablets [redacted] of API was available for injection even after preparing the sample in 2 mls. High viscosity prevented the aspiration of reformulated OxyContin when prepared with 2 ml of water.

Figure 5.1 Syringability results-

Volume expelled and mg of API recovered by tablet strength, syringe volume and needle gauge

(b) (4)

[redacted]

Figure 5.1 (continued) Syringability results-

Volume expelled and mg of API recovered by tablet strength, syringe volume and needle gauge

Injectability

As shown in **Figure 5.2 A**, injecting a solution of material at room temperature with a 27 gauge needle allows for [redacted] to be injected. This is consistently seen regardless of the volume of the preparation. Boiling the sample before preloading the syringe, as shown in **Figure 5.2 B** increases the amount of API in the extrudate [redacted]); in this case the sample volume is [redacted]. For all of the conditions tested, tablet strength was not shown to be a contributing factor, meaning the difficulty observed in expelling the material was not conditional on the tablet strength.

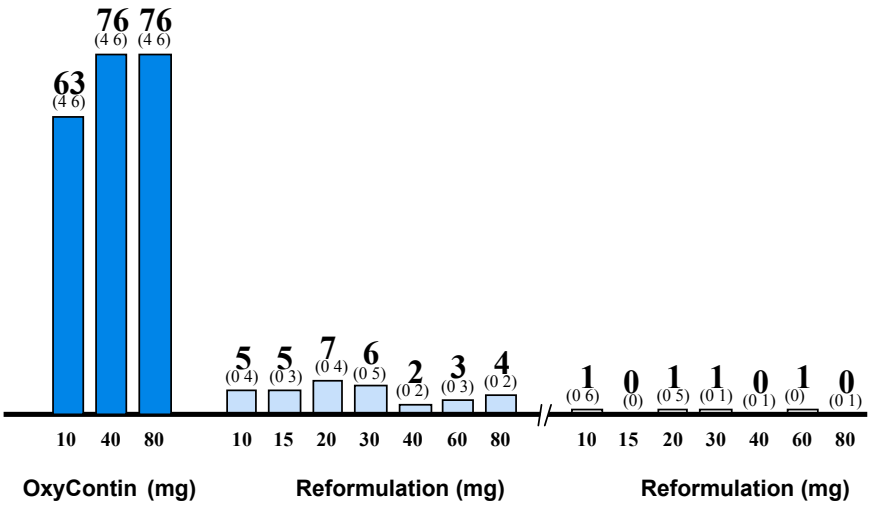
To better understand how the reformulation performs under a wide range of conditions [redacted] needles were evaluated for injectability. Using an [redacted] resulted in a significant improvement in recovering material after injection. The amounts of preparatory volume or temperature did not result in significant differences in the amount of API expelled [redacted] once this gauge needle was used. Results for [redacted] syringe are found in **Figure 5.2 C-D**. These results can be compared to those obtained with OxyContin, which is easily expelled in all conditions delivering [redacted] label claim API through a [redacted] (b) (4).

Figure 5.2 Results for injectability
(% of API and ml of volume expelled)

Injectability – (b)

% API expelled (ml)

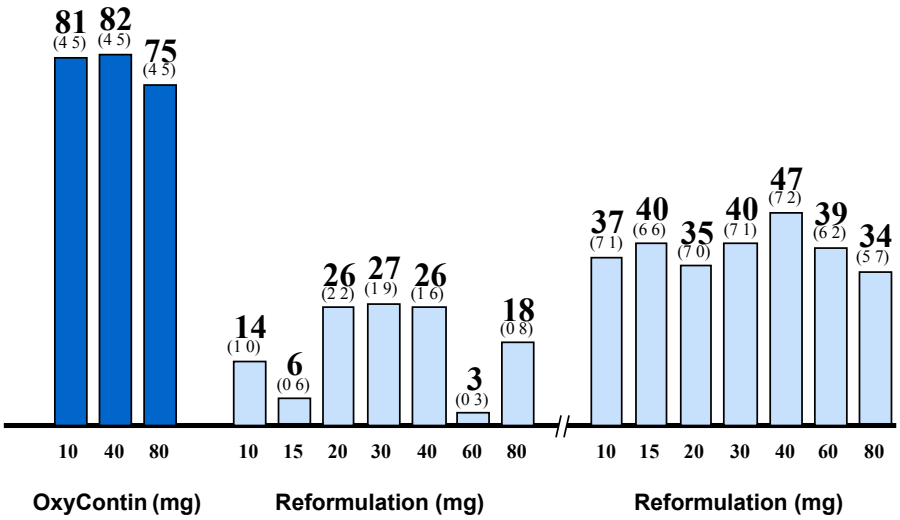
A



Injectability –

% API expelled (ml)

B



(b) (4)

(b) (4)

Extraction after vaporization

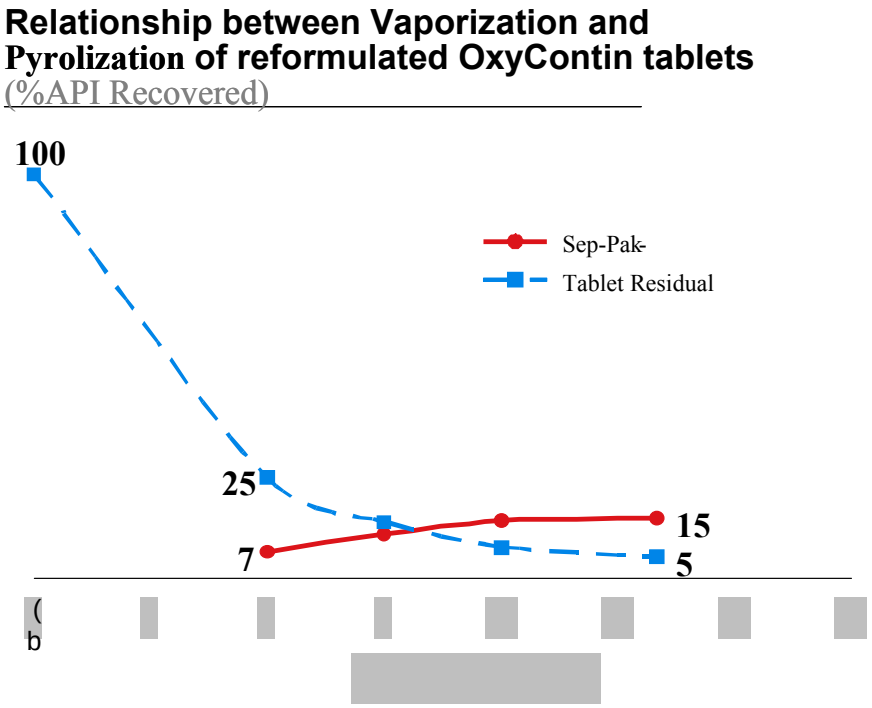
Figure 5.3 A-B, show the results of optimization studies performed to determine the relationship between the vaporization of API and the degradation of API through pyrolization. This figure shows that as the amount of vaporized API increases for reformulated or current OxyContin, the amount of residual API rapidly decreases. It is difficult to because of the proximity of the vaporization and degradation temperatures) of oxycodone HCl, the salt form of oxycodone. In the case of reformulated OxyContin, API can not be vaporized possibly due to interference from the excipient. Therefore, the analysis for reformulated OxyContin was performed at which is just below the . As shown in **Figure 5.3 A-B**, the final amount of oxycodone HCl vaporized for both OxyContin or reformulated OxyContin is No residual API in the analysis tube was found suggesting pyrolization of the remaining API. Using the data shown in **Figure 5.3 A-B**, the optimum analysis times were determined to be and (b) (4) OxyContin.

(b) (4)e was used as a positive control. The melting point of oxycodone (b) (4), and much of the API can be vaporized without degradation. Approximately 70% vaporization efficiency was achieved in (b) (4) after which no API remains in the analysis tube.

Figure 5.3 C shows the amount of API recovered from vaporized samples under optimal time and temperature conditions. As shown in this figure, [redacted] of all strengths of reformulated OxyContin results [redacted] after [redacted] of heating. Results for OxyContin [redacted] This is likely related to the higher vaporization temperature of the salt (HCl) form of the drug. Oxycodone [redacted] has a lower vaporization temperature and yields a far higher vaporization efficiency of [redacted]

Figure 5.3 Relationship between vaporization and pyrolization

A



B

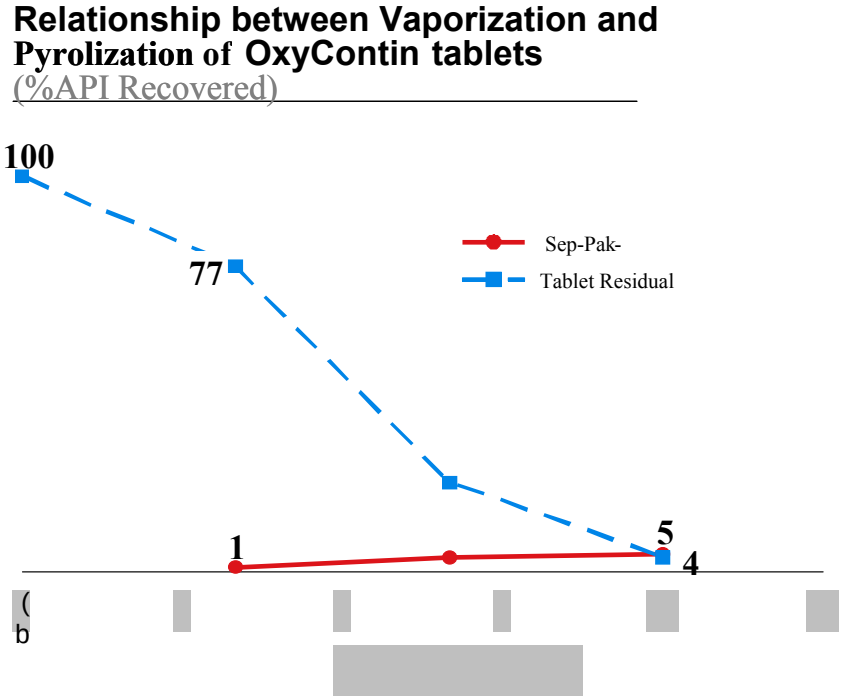


Figure 5.3 (continued)

Discussion

Syringability

Syringability preparations of reformulated OxyContin tablets result in difficult aspiration conditions and yield low drug delivery. This is due to the viscosity of polyethylene oxide after hydration. Larger preparatory volumes are necessary to counter the viscosity of the solution. However, this is counterproductive for an abuser as the solutions become increasingly dilute.

To yield higher API, [redacted] volumes are required for injection. Reformulated OxyContin could only be syringed with [redacted]. Furthermore although solutions could be syringed with an [redacted] the resulting solution is highly viscous, likely deterring intravenous injection.

Injectability

Backfilling a syringe is not likely amenable to abuse due to the [redacted] after hydration. The [redacted] renders the preparation of reformulated OxyContin tablets [redacted] and unattractive as a preparation for intravenous injection. Very little API could be pushed through a [redacted], even with significant force. The use of an [redacted] resulted in the extrusion of higher amounts of API.

However, large bore needles are not readily available to the general public. Boiling aided in the amount of sample expelled. To do this study the syringe had to be backloaded and immediately injected with [redacted] (b) (4) solution. This would require a potential abuser to inject molten hot material, which is undesirable and uncomfortable. [redacted] As the temperature of a boiled solution [redacted] (b) (4), the material becomes [redacted]

STUDY 6:

(b) (4)

(b) (4)

Table 6.2

(b) (4)

STUDY 7: (b) (4)

(b) (4)

(b) (4)

(b) (4)

Additional information

CONTENTS OF NDA 22-272 RESUBMISSION TO FDA

NDA 22-272 for reformulated OxyContin was resubmitted to FDA on March 30, 2009 and included five main elements:

- Pharmacokinetic data demonstrating bioequivalence of the current and reformulated OxyContin
- *In vitro* testing on reformulation's physicochemical properties
- Stability and other CMC data for all tablet strengths, including 60 and 80 mg strengths
- Proposed label, without reference to "tamper resistance" or improved physical properties
- Interim risk evaluation and mitigation strategy (REMS) proposal

BIOEQUIVALENCE OF REFORMULATED OXYCONTIN

Reformulated OxyContin met strict bioequivalence criteria and, as a result, is therapeutically interchangeable with the current formulation of OxyContin for patients when used as directed. Cmax mean ratio observed was 97.0 (with 90% CI limits of 93.11, 101.13) and AUCt mean ratio was 95.2 (with 90% CI limits of 92.48, 97.93) (see **Figure 8.1**, **Table 8.1**).

Figure 8.1 Pharmacokinetic data demonstrating bioequivalence of current and reformulated OxyContin

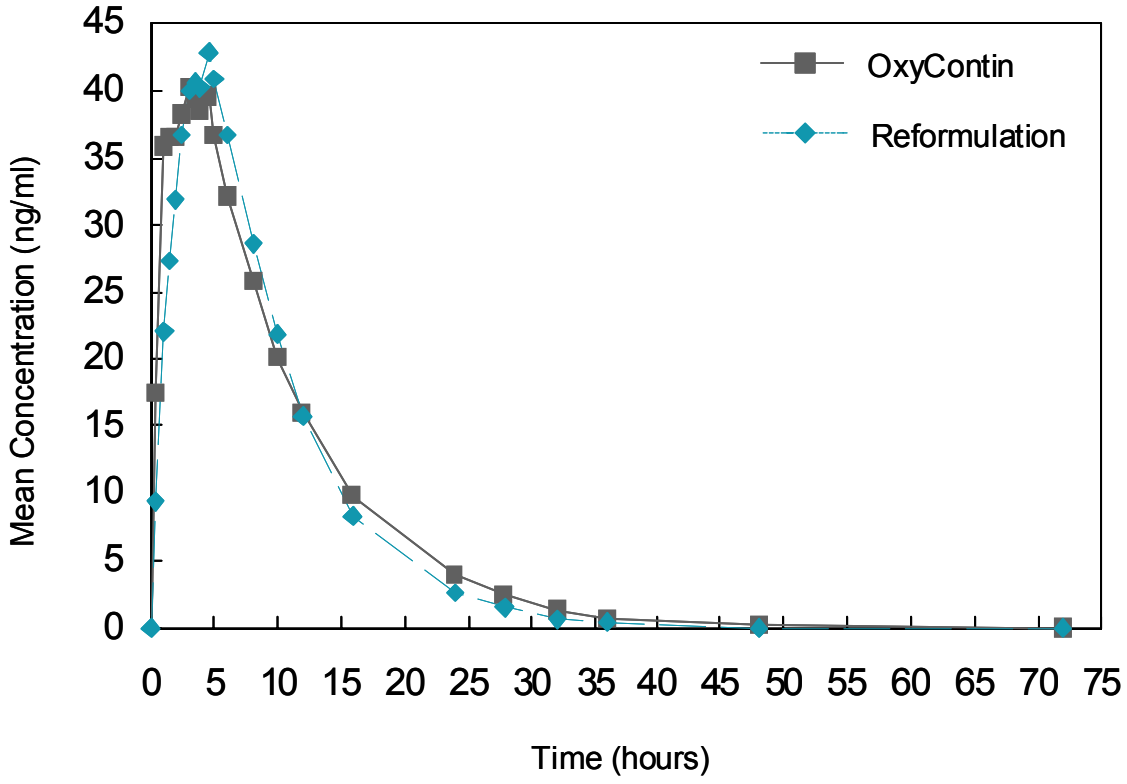


Table 8.1 Summary of pharmacokinetic results following oral administration of reformulated versus current formulation OxyContin in the fed and fasted states

			Cmax		AUCt	
Study	**Dose**	**Condition**	**LS Mean Ratio**	**90% CI**	**LS Mean Ratio**	**90% CI**
OTR1002	10 mg	Fed	105	(101.06, 108.51)	95.7	(93.85, 97.68)
OTR1003	10 mg	Fasted	102	(99.35, 105.42)	98.3	(95.20, 101.48)
OTR1004	40 mg	Fed	99.9	(95.40, 104.52)	92.6	(90.13, 95.13)
OTR1005	40 mg	Fasted	97.0	(93.11, 101.13)	95.2	(92.48, 97.93)
OTR1008	80 mg	Fed	110	(105.21, 114.47)	94.9	(92.90, 97.02)
OTR1009	80 mg	Fasted	103	(98.67, 106.66)	97.1	(94.41, 99.94)
			PK Metric	**Slope**	**90% Conf. Interval (Power Model)**	**Critical Range (Power Model)**
OTR1006 Dose proportionality	10-40 mg	Fasted	Cmax	1.06	(1.03, 1.09)	(0.8390, 1.1610)
			AUCt	0.963	(0.940, 0.987)	
OTR1012 Dose proportionality	40-80 mg	Fasted	Cmax	0.845	(0.771, 0.919)	(0.6781, 1.3219)
			AUCt	0.970	(0.910, 1.03)	

RISK MITIGATION

Although comprehensive preclinical work and data from *in vitro* experiments are meant to reduce the uncertainties associated with this reformulation, further risk mitigation measures are necessary to ensure that the benefits of the product continue to outweigh the risks associate with its use. Forecasting post-marketing clinical outcomes, with a high degree of precision, on the basis of *in vitro* experiments or other pre-marketing studies is not currently possible. The uncertainties inherent in predicting the outcomes associated with the introduction of a new or reformulated product into the market with only pre-approval data need to be addressed by balancing the potential risks with the product's clear benefits. This is especially important to guide us forward in the absence of relevant precedent. Therefore in parallel to developing and executing the *in vitro* experimental studies, we have engaged experts to explore and develop programs that will enable us to mitigate the risks associated with the uncertainties.

REMS have become a significant topic for discussion and development since the May 5, 2008 Advisory Committee meeting. The nature of diversion, misuse and abuse of therapeutic medications make it evident that comprehensive strategies and approaches are necessary across all opioids. Purdue has taken an active and significant role in an Industry Working Group of over 20 branded and generic companies that is driving towards creation of a collective proposal to the FDA for a class-wide REMS for modified-release and long-acting opioids. This group has been meeting regularly since April 2009 and has made significant progress. A summary of

the work from this group was presented during the May 27-28, 2009 opioid REMS open meeting.

While individual sponsors actively develop formulations that represent important incremental improvements in robustness and pursue hypothesis-driven risk mitigation approaches specific for products, many larger questions about risk need to be answered collectively by all stakeholders involved (i.e., how to measure unintended consequences, education about risks and benefits, monitor use, etc.). Purdue has independently made consistent and growing investments in a number of efforts to mitigate abuse and diversion risk, but we recognize that this is not enough.

We consider the discussion of risk management to be critically important in the overall approach to introducing a reformulation. However, based on guidance from FDA this document has not discussed risk management and rather focused on providing Advisory Committee members an overview of the *in vitro* studies conducted. The interim REMS proposal for the period before a opioid classwide RES is in place for reformulated OxyContin is the subject of a separate discussion with FDA.

Discussion

IMPLICATIONS OF *IN VITRO* TESTING RESULTS

The studies described in this document assessed the characteristics of reformulated OxyContin tablets when subjected to tampering procedures such as crushing, powdering, and extraction methods that are practiced, or may be attempted with OxyContin and other opioids. Reformulated OxyContin was shown to be demonstrably more difficult to crush than current OxyContin and [redacted]. Given that oral abuse of OxyContin is the most common route of administration, the added hardness and hydrogelling properties of the reformulation are incremental improvements when compared to the current formulation of OxyContin, however this will require further study. Intranasal misuse also is frequently reported for OxyContin. The hydrogelling properties of reformulated OxyContin are likely to discourage abuse and misuse by this route. In order for API to be absorbed after insufflation, powdered insufflated material must be moistened in order for the active ingredient to cross the capillary barrier. Upon contact with moisture the reformulated OxyContin hydrogels, which as demonstrated by our data, is expected to retard the release of API. In comparison with current OxyContin where hydrogelling does not occur, drug release after insufflation of hydrogelled reformulated OxyContin is expected to be slower. These differences in kinetics of API release as well as the viscosity and physical appearance of hydrogelled powder will likely discourage abuse and misuse by this route. A smaller number of misusers extract OxyContin for

injection. The ability to extract oxycodone from the reformulation is more difficult and requires a greater expenditure of time or effort to prepare a solution for injection, as well willingness to inject large volumes and/or to use a large bore needle (e.g., 18 gauge, which is not commonly available). The effects of alcohol (ethanol) co-administered with reformulated OxyContin tends to retard release, rather than enhancing it as demonstrated in dissolution tests.

ANTICIPATED IMPACT ON MISUSE AND ABUSE

As mentioned above, the *in vitro* data presented in this report alone do not allow Purdue to accurately (quantitatively) predict the impact of this reformulated product on abuse and other "real world" outcomes. However, these in vitro data *do* provide the basis for a qualitative or directional prediction of these "real world" outcomes once this reformulated product is introduced to the market. For example, the *in vitro* data described below indicate that the physical properties of the reformulation will minimize or eliminate inadvertent misuse by crushing, make intravenous abuse difficult if not impossible via a common insulin syringe, render insufflation likely less attractive and yield very little API via smoking.

Despite the utility of these *in vitro* data, pre-marketing assessments whether in the lab or clinical study setting are of limited predictive value. For example, it is not possible to accurately predict unintended consequences of introducing reformulated OxyContin in terms of potential shifts to the use of other drugs (e.g. methadone, heroin). In addition, *in vitro* data cannot predict the impact of the reformulation on oral abuse of intact

tablets. Therefore, although these pre-marketing data guide us in our understanding of how certain populations may be less likely to misuse (intentionally or unintentionally) and abuse this formulation, we are unable to state with any level of certainty how the patterns will shift and if the total "denominator" of abuse will change.

In addition to insights gained regarding the improvements made by reformulating OxyContin, our *in vitro* experiments were designed to explore the limitations of the reformulation. All experimental scenarios were carried out to the point that all API or no further API was released with additional time. This means that the endpoints were specifically designed to demonstrate the time or effort necessary for the complete release of oxycodone by defeating the controlled release mechanism. We compared the physical properties of the reformulation to current OxyContin under anticipated abuser tablet manipulation scenarios. In most tablet manipulation simulations tested, the reformulated product was demonstrated to be more resistant to physicochemical tablet manipulation than the current formulation. Further, despite extensive testing we could not identify any new or unexpected vulnerabilities of the reformulation.

PURDUE'S INTENT

Our goal is to help address the ongoing public health problem of prescription opioid abuse by introducing a reformulation that is an incremental improvement for both patient and non-patients. We do not intend to use this reformulation as a basis for targeting or broadening the

patient population by suggesting enhanced safety, tamper resistance, or abuse resistance or deterrence in the absence of evidence supporting such claims. Accordingly we will:

- **Stop shipping the current formulation of OxyContin as soon as all tablet strengths (10-80 mg) of the reformulated product have been approved and are available for shipping.** Based upon our ability to maintain low levels (approximately 2-3 weeks) of original formulation inventory at the wholesaler level, we expect the transition from marketed OxyContin to reformulated OxyContin at the individual patient level to occur within approximately 6-8 weeks of shipping. Inventory of the old formulation in the pipeline will be managed to an extremely low level to minimize the availability of both formulations in the market at the same time. We expect that 90% of the current formulation will be switched within approximately two weeks. We will do this in a manner designed to minimize confusion and disruption to physicians, pharmacists and patients.

- ***Not seek label claims related to "tamper resistance," "abuse resistance," or "abuse deterrence" of the reformulated tablets.*** While small changes to the label are necessary to reflect the substitutions in tablet excipients of the reformulation and to provide new summary pharmacokinetic data, we want to avoid intentional or unintentional messaging that this reformulation offers advantages over the existing OxyContin formulation. We do not intend to use this reformulation as grounds for targeting or broadening the patient population on the basis of enhanced patient safety or resistance to tampering. In contrast to our position in May 2008, we now realize

that it is not possible to scientifically predict the impact that improvements in physical properties of any abused prescription medication will have on "real world" abuse, no matter how large the improvements ("deltas") observed via *in vitro* testing or any other pre-approval testing are. Purdue will only consider requesting "tamper resistance" labeling with the availability of supportive post-marketing epidemiological data. This data must describe and quantify the impact of the reformulation on different segments of OxyContin abuse and misuse.

- ***Retain the current OxyContin trade name.*** We intend to retain OxyContin trade name for the reformulation in order to avoid confusion on the part of the patient, pharmacist and physician regarding the nature of the product being prescribed or dispensed. Additionally, a change to the trade name would require announcements, new labeling and new promotional materials, with the associated publicity that could have the unintended potential of conveying precisely the message we are planning to avoid – that a "new and improved" formulation lacking the risks understood to be associated with OxyContin is being introduced.

Concluding remarks

Reformulated OxyContin is bioequivalent to current OxyContin, as defined by strict bioequivalence criteria. As a result, the new formulation is

therapeutically interchangeable with the current formulation for patients when used as directed.

No therapeutic product is completely immune from sophisticated tampering methods, but reformulated OxyContin tablets present a higher barrier to physicochemical tampering compared to the current formulation. The reformulation increases the amount of time or effort that misusers and abusers must expend to overcome its controlled-release mechanism to extract oxycodone API to achieve a “high”. The *in vitro* experimental studies described above demonstrated this incremental improvement over the current formulation.

Our experimental results suggest that the reformulated tablets will be more difficult to accidentally misuse by crushing, more difficult or impossible to abuse intravenously using a common insulin syringe, likely less attractive to abuse via insufflation and yield very little API when smoked. Furthermore these data show that the reformulation is not more susceptible to tablet manipulation than OxyContin under any testing condition. The scientific quality and scale of these studies map the terrain of the potential outcomes of abuse and misuse to an unprecedented level, enabling future hypothesis-driven risk mitigation strategies.

We hope that this document has been helpful in briefing members of the Advisory Committee on the *in vitro* testing work that Purdue has recently completed.

Glossary of Terms

Abuse: The use of a drug in a manner detrimental to the individual or society but not meeting criteria for addiction.

"Advanced" solvents: Refers to solvents that are organic and not directly ingestible

API: active pharmaceutical ingredient.

Also referred to as **particle bands** and **particle fractions**.

Dissolution: Refers to testing designed to assess the rate of API release in a large volume of solvent (b) (4)

Dose dumping: Refers to a phenomenon sometimes observed in other abused controlled-release prescription tablets in which accelerated release of **API** from the controlled-release mechanism is observed. In this document "dose dumping" specifically refers to accelerated release of API in ethanol solvent.

Excipient: An inactive substance added to pharmaceutical tablets as a carrier for the **API**. In the case of **reformulated OxyContin** tablets the primary excipient **PEO** is used to provide a controlled-release mechanism, and (after curing) confer the improved physical properties of crush-resistance and hydrogelling in small volumes of solvent.

Extraction: Refers to testing designed to assess the rate of API release in a small volume of solvent (30 ml).

Free-basing: The conversion of an API or illicit drug substance from its water-soluble salt form (e.g., cocaine-HCl) to its standalone basic form of an amine (usually an alkaloid natural product, e.g., "crack-cocaine").

Household Solvents: Refers to solvents that are ingestible and/or are easily obtainable (cooking oil, ethanol, water, coke and saline).

Hydrogel: Process by which particles or whole **reformulated OxyContin** tablets become highly viscous in small volumes of solvent (property conferred by the **PEO** excipient matrix).

Insulin syringe: 1 ml syringe with a 28 gauge needle. This is the most commonly available type of syringe, most likely to be used by abusers interested in abusing via intravenous route of administration. Also referred to as a **tuburculin syringe**.

Injectability: Refers to the ability of a material to be expelled from a syringe through a needle (as it would be in an injection).

***in vitro* experimental studies:** Refers to the *in vitro* experiments described in this report. These studies tested the robustness of the controlled-release mechanism of **reformulated OxyContin** tablets under scenarios of known and anticipated abuser tablet manipulations in the "real world" ("tamper testing") and was designed in response to the FDA's October 3, 2008 Complete Response Letter to Purdue.

Mechanical fractionation: Refers to mechanical reduction of tablets to smaller particles. Also referred to as **particle size reduction**.

Misuse: The exposure resulting from the use of a prescription medication in ways other than how it was prescribed, contrary to approved labeling unless taken as directed by a healthcare provider, and below the threshold of abuse.

Particle bands: (see **bands**)

Particle fractions: (see **bands**)

Particle size reduction: (see **mechanical fractionation**)

Polyethylene oxide (PEO): PEO is the main excipient of **reformulated OxyContin** tablets.

Reformulated OxyContin: Also referred to as **the reformulation**. Refers to the bioequivalent reformulation of OxyContin tablets. The currently marketed formulation is referred to throughout this document as OxyContin.

RT: Room temperature (25 ºC).

SGF: Simulated gastric fluid media.

Syringability: Refers to the ability of a material to be loaded into a syringe by withdrawing the plunger and pulling it through the needle (as it would be in preparing a syringe for an injection).

Tampering: Chemical and/or physical alteration of a prescription medication contrary to approved labeling.

Tuberculin syringe: 1 ml syringe with a 28 gauge needle. This is the most commonly available type of syringe, most likely to be used by abusers interested in abusing via intravenous route of administration. Also referred to as an **insulin syringe.**

Vaporization: Refers to extraction of API by dry heating, simulating conditions used in abuse by an inhalation smoking route of administration.

Appendices

I. Experts consulted external experts
II. Detailed methodology
III. *in vitro* testing methodology

PURDUE PHARMA L.P.

RESEARCH & DEVELOPMENT

September 24, 2009

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Appendix I:

Experts Consulted

EXPERTS CONSULTED ON MODES OF ABUSE AND MISUSE:

Sandra Comer, PhD

- Associate Professor of Clinical Neurobiology, Division on Substance Abuse, Columbia University

Ed Cone, PhD

- Adjunct Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine

Herb Kleber, MD

- Professor of Psychiatry, Columbia University
- Director, Division on Substance Abuse, Columbia University

Ed Sellers, MD, PhD

- Professor of Pharmacology, Medicine and Psychiatry, University of Toronto

Jim Zacny, PhD

- Professor of Anesthesia & Critical Care, University of Chicago

EXPERTS CONSULTED ON "PHYSICO-CHEMICAL METHODS OF DRUG TAMPERING":

Bob Bianchi

- President, Bianchi Consulting, Ltd.
- Vice President and Chief of Scientific and Technical Affairs, Prescription Drug Research Center
- Former Laboratory Director, Drug Enforcement Administration, (DEA)

Ed Cone, PhD

- Adjunct Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine

EXPERTS CONSULTED FOR REMS ISSUE ANALYSIS AND CONCEPT DESIGN:

Bob Bianchi

- President, Bianchi Consulting, Ltd.
- Vice President and Chief of Scientific and Technical Affairs, Prescription Drug Research Center
- Former Laboratory Director, Drug Enforcement Administration, (DEA)

Michael J. Brennan, MD

- Medical Director, Pain Center of Fairfield
- Senior Attending Physician & Section Chief, Division of Pain Management & Rehabilitation, Bridgeport Hospital

Bruce Burlington, MD

- Sole Proprietor, DB Burlington Associates
- Former Head of Regulatory Affairs, Wyeth
- Former Deputy Director Med Affairs, FDA
- Former Head of Investigational New Drugs Division (Center of Biologics), FDA
- Former Head of Center for Medical Devices and Radiological Health, FDA

Ronald W. Buzzeo, RPh

- Chief Regulatory Officer, Cegedim Dendrite Compliance Solutions

Ed Cone, PhD

- Adjunct Professor of Psychiatry, Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine

Perry Fine, MD

- Professor of Anesthesiology, University of Utah
- Associate Medical Director, Pain Management Center

Jack Henningfield, PhD

- Professor of Behavioral Biology, Johns Hopkins University School of Medicine
- Vice President Research & Health Policy, Pinney Associates

James Hill, RPh, MBA

- President, Pharmacy Strategy Group

Nathaniel P. Katz, MD, MS

- President, Analgesic Research Services

Kevin Nicholson, RPh, JD

- Vice President of Pharmacy Regulatory Affairs, National Association of Chain Drug Stores (NACDS)

John M. Pinney

- Founder and President, Pinney Associates

Bruce T. Roberts, RPh

- Executive Vice President, National Community Pharmacists Association (NCPA)

Will Rowe

- Patient Advocate
- Chief Executive Officer, American Pain Foundation

Sidney H. Schnoll, MD, PhD

- Clinical Professor of Internal Medicine and Psychiatry, Medical College of Virginia
- Vice President Pharmaceutical Risk Management Services, Pinney Associates
- Former Chairman of the Division of Substance Abuse Medicine, Medical College of Virginia

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Appendix II:

In Vitro Testing Methodology

OVERVIEW

As mentioned in the main **Briefing Document**, the seven studies described below were designed in consultation with experts in drug abuse, abuser tampering methods and analytical pharmaceutics (see **Appendix I**) in order to address the concerns raised by FDA in the October 3, 2008 Complete Response Letter. After internal validation of the protocols to ensure reproducibility and consistency across Studies, methods were standardized and transferred to contracted third party vendors.

The majority of experiments were performed by two contracted independent third party vendors (Aptuit, Kansas City, MO and Catalent Pharma Solutions, Research Triangle Park, NC). Study 1, Study 6 and Study 7 were performed in Purdue labs. Both Catalent and Aptuit met the required standards and data agreement from multiple analysts. Personnel performing the experiments were blinded to the extent possible. Division of work between these two vendors was capacity-driven, with a goal to complete the all seven Studies as expeditiously as possible. Upon completion of the studies, both an independent third party vendor (IHL Consulting Group, Loganville, GA) and internal Purdue staff performed extensive quality assurance analysis of the resulting data.

Samples in all extraction and dissolution experiments were analyzed following pre-specified HPLC conditions provided to the CROs in a separate protocol that is not covered in this document. These conditions were previously validated for the GMP analysis of reformulated OxyContin 10 – 80 mg tablets.

The methodology for each Study is summarized below. More detailed protocols than the methods described here were prepared for the CRO vendors.

STUDY 1: (b) (4) FRACTIONATION OF TABLETS

Table 1.1 to API ratios for all tablet strengths of reformulated OxyContin

Tablet strength (mg)	per tablet	(b) (4) : API ratio
10	138.50	13.9
15	133.50	8.9
20	128.50	6.4
30	118.50	4.0
40	108.50	2.7
60	162.75	2.7
80	167.50	2.1

STUDY 2: EXTRACTION IN (b) (4) (b) (4) SOLUTIONS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Statistical analysis

The same statistical methods were applied across all simple extraction experiments for water [redacted] solvents and [redacted] (b) (4). The average API release across all tablet strengths for each testing condition (solvent and temperature) were plotted over time (average API release on the y-axis and time on the x-axis). A line was plotted for each particle size band within each testing condition. Significant differences between bands were assessed by comparing them using a two way analysis of variance (with fixed terms for particle band, tablet strength, and (band * strength)) followed by Duncan's multiple comparison of bands at the two sided 5% level. Individual replicates were also analyzed in this way.

STUDY 3: DISSOLUTION IN ETHANOL

The method used for the dose dumping dissolution studies was previously validated for the GMP analysis of reformulated OxyContin 10 – 80 mg tablets (not described in this document) and used in the original tamper testing experiments included in the November 29, 2009 NDA submission and discussed at the May 5, 2008 Advisory Committee meeting. In brief dissolution of tablets was carried out using USP Apparatus 1 (Baskets) at without enzymes (b) (4) maintained at (b) (4). The dissolution vessels were covered at all times.

The number of replicates used in this study for reformulated OxyContin was determined statistically through data generated internally from dissolution of bands 2 (b) (4)), 4 ((b) (4) 5 (b) (4) and 6 (b) (4) of reformulated OxyContin 80 mg sample (n=3) in (b) (4) at (b) (4) Standard deviations of the triplicates were calculated at (b) (4) (b) (4). The average of the 20 standard deviation was determined to be 9.0. It was decided that knowing the true mean of a particular solvent/band/time within 10% label claim was acceptable. With a standard deviation of 9.0, when the sample size is equal to 6, the 95% confidence interval for the mean is ± 9.5. Thus it was estimated that a sample size of 6 would result in the observed mean being within 10% label claim of the true mean.

The test materials used in this study are found in **Table 3.1**.

Table 3.1 Test materials for Study 3 – dissolution in ethanol

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1F61	Reformulated OxyContin	10
W1H71	Reformulated OxyContin	40
W1G71	Reformulated OxyContin	80
CW79D0 (core)	Reformulated OxyContin (uncured core powder)	80

Catalent Pharma Solutions, Raleigh, North Carolina, an independent contract research organization conducted this Study. Capability quality assurance in HPLC and executing the dissolution extraction procedures was performed according to separate protocols provided for the CRO. The CRO met the required standards and data agreement from multiple analysts.

Statistical analysis

The dissolution profiles of the API release in (b) (4) and (b) (4) were compared for each tablet strength and each particle size band with the similarity factor f2 (Supac-MR:Modified Release Solid Oral Dosage Forms, FDA guidance, Sept 1997, pages 32-33). The calculation is

$$f2 = 50 \log10\{[1+1/n \sum(R-T)^2]^{-0.5} \times 100\}$$

An f2 value of 50 or greater indicated similarity in dissolution profile. The maximum time point included for statistical analysis was chosen such that each analysis included at least three time points and only one dissolution time point after API release plateaus.

STUDY 4: EXTRACTION IN ADVANCED SOLVENTS

The sample size for reformulated OxyContin was determined statistically through data generated internally from extraction of bands 2 (b) (4) 4 (b) (4)), 5 (b) (4)) and 6 (b) (4)) of reformulated

OxyContin 80 mg sample (n=2) in (b) (4) at (b) (4) . Standard deviations of the duplicates were calculated at (b) (4) extraction time. The average of the 24 standard deviation was determined to be 7.5. It was decided that knowing the true mean of a particular solvent/band/time within 10% label claim was acceptable. With a standard deviation of 7.5, when the sample size equal to 5, the 95% confidence interval for the mean is ± 9.3. Thus it was estimated that a sample size of 5 would result in the observed mean being within 10% label claim of the true mean. For OxyContin, the sample can be rendered to powder easily and the data generated is consistent, therefore, a sample size of n=3 was sufficient.

Catalent Pharma Solutions, an independent contract research organization in Raleigh, North Carolina, conducted this Study. Capability and qualification in HPLC and executing the small volume extraction procedures was performed according to separate protocols provided for the CRO. The CRO met the required standards and data agreement from multiple analysts.

Table 4.1 Materials and conditions for Study 4 – extraction in advanced solvents

Tablet strength	Reformulated OxyContin lot number	OxyContin lot number	Testing conditions
10 mg	X1LY0	W1B71	All solvents
15 mg	X1MG0	n/a	All solvents
20 mg	X1MH0	n/a	All solvents, ,
30 mg	X1MJ0	n/a	All solvents, ,
40 mg	X1LK0	W0S71	All solvents,
60 mg	X1MK0	n/a	All solvents, ,
80 mg	X1LL0	W0Y61	All solvents, ,

[redacted]

Statistical analysis

Results with advance solvents were statistically analyzed in the same way as described above for small volume extractions with water, [redacted] (b) (4) solvents and [redacted] (b) (4) Average API release across all tablet strengths for each testing condition (solvent and temperature) were plotted over time (average API release on the y-axis and time on the x-axis). A line was plotted for each particle size band within each testing condition. Significant differences between bands were assessed by comparing them using a two way analysis of variance (with fixed terms for particle band, tablet strength, and (band * strength)) followed by Duncan's multiple comparison of bands at the two sided 5% level. Individual replicates were also analyzed in this way.

STUDY 5: SYRINGABILITY, INJECTABILITY AND EXTRACTION AFTER VAPORIZATION

As noted by Dr. Edward Cone in **Appendix III**, (b) (4)) needles are most commonly used for the purpose of abuse by intravenous injection. For practical purposes, needles were used for this study except for a series of testing that was previously performed and submitted in the original NDA. This former testing used common insulin syringes (b) (4), (b) (4)) and a preparatory volume (b) (4)

Aptuit, Inc., an independent contract research organization in Kansas City, Missouri, conducted this Study. Capability and qualification for HPLC analysis and for syringability procedures were performed under a separate protocol prepared for the CROs (not covered in this document).

The test materials used in this study are found in **Table 5.1.**

Table 5.1 Test materials for Study 5 – syringability testing

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1B71	OxyContin	10
W0S71	OxyContin	40
W0Y61	OxyContin	80

Aptuit, Inc., an independent contract research organization in Kansas City, Missouri, conducted this Study. Capability and qualification for HPLC analysis and for injectability procedures were performed under a separate protocol prepared for the CROs (not covered in this document).

The test materials used in this study are found in **Table 5.2.**

Table 5.2 Test materials for Study 5 – injectability testing

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1B71	OxyContin	10
W0S71	OxyContin	40
W0Y61	OxyContin	80

Aptuit, Inc., an independent contract research organization in Kansas City, Missouri, conducted this Study. Capability and qualification for HPLC analysis and for smoking simulation procedures were performed under a separate protocol prepared for the CROs (not covered in this document).

The test materials used in this study are found in **Table 5.3.**

Table 5.3 Test materials for Study 5 – extraction after vaporization

Test article	Formulation	Tablet strength (mg)
X1LY0	Reformulated OxyContin	10
X1MG0	Reformulated OxyContin	15
X1MH0	Reformulated OxyContin	20
X1MJ0	Reformulated OxyContin	30
X1LK0	Reformulated OxyContin	40
X1MK0	Reformulated OxyContin	60
X1LL0	Reformulated OxyContin	80
W1B71	OxyContin	10
W0S71	OxyContin	40
W0Y61	OxyContin	80
Oxycodone base	Pure API	N/A

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Appendix III:

Comment on Purdue In Vitro Testing Studies Written by Dr. Edward Cone

Rational Approach to Tamper Assessment and Experimental Design: An Introduction

Edward J. Cone, Ph.D.

PinneyAssociates

March 6, 2009

Executive Summary

Although OxyContin® is used by millions of Americans for the relief of moderate to severe pain, nonmedical use, or misuse, contributes to the problem of illicit drug use. When used as intended, OxyContin®'s controlled release mechanism slowly releases oxycodone over a period of 12 hours, providing safe and effective pain relief. But cutting, crushing or chewing OxyContin® overcomes the controlled release mechanism and releases most of the oxycodone dose making it similar to an immediate release product. Crushing an OxyContin® tablet provides nonmedical users the opportunity to administer the entire dose immediately either by the oral or by the intranasal route. Crushed and powdered OxyContin® tablets also can be readily dissolved for injection, increasing the risk of overdose and death. Misuse of OxyContin® with other central nervous system depressants results in an increase in OxyContin® related deaths.

Purdue Pharma L.P. has developed a reformulation of OxyContin®, which will replace all current strengths of the current product. Reformulated OxyContin® incorporates new technology that provides significant improvements in tamper resistance. Unlike OxyContin®, which can be crushed with a spoon or other implements in a matter of seconds, the reformulation is only deformed by most manual methods, and requires electric mills or blenders for reduction to a fine powder. Even when crushed successfully, it retains a major portion of its controlled release properties. In addition, reformulated OxyContin® forms a viscous hydrogel when hydrated. It is anticipated that the gel formation will be a significant detriment to use by the intranasal route. Further, viscous gel formation occurs in small volumes of water, making it difficult if not impossible to prepare for injection. Even when successfully powdered, the reformulation continues to retain some controlled release properties. The reduced release of oxycodone from the reformulated OxyContin® tablet (compared to current OxyContin®) in water and other solvents is expected to retard tampering efforts by crushing and extraction.

Development of tamper assessment protocols for *in vitro* testing of reformulated OxyContin® was undertaken in consultation with experts experienced in drug abuse treatment and tampering methods and experts knowledgeable in extraction techniques. Scientific literature and Internet reports were reviewed for information on methods of tampering with OxyContin® and other opioid formulations. This information was used to develop a comprehensive series of laboratory-based *in vitro* assessment protocols for evaluation of the "tamper resistant" properties of reformulated OxyContin®. The scope of these protocols covered commonly known methods of tampering with oral opioid formulations as well as methods that were considered likely to be attempted by experienced tamperers. The experimental design of each protocol included the following elements considered necessary to yield reliable scientific data:

- Testing of all dose strengths of reformulated OxyContin®
- Testing methods extended to determine failure limits
- Inclusion of adequate controls for comparison to current OxyContin®
- Sufficient replicates for evaluation of method variability
- Method validation procedures
- Investigation of a range of conditions on outcome of results, e.g., temperature, time
- Use of independent laboratories
- Testing under blind conditions to the extent possible

Each protocol was developed to address at least one method or component of common tampering attempts currently employed or predicted to be employed with reformulated OxyContin®. Specifically, *in vitro* tests were designed to provide an accurate assessment of the potential for reformulated OxyContin® to be tampered with for the following types of misuse:

a. Crushability: chewing, cutting, grinding, powdering

b. Swallowing: chewed or powder (dissolution)

c. Effect of co-consumption of alcohol on “dose dumping”

d. Extraction (simple and complex methods)

e. Injection (syringeability and injectability)

f. Nasal insufflation (snorting/sniffing)

g. Smoking

The results of these assessments of reformulated OxyContin® provide detailed, valid scientific data on the strengths and weaknesses of the reformulation when subjected to current and potential future tampering attempts across a broad range of conditions.

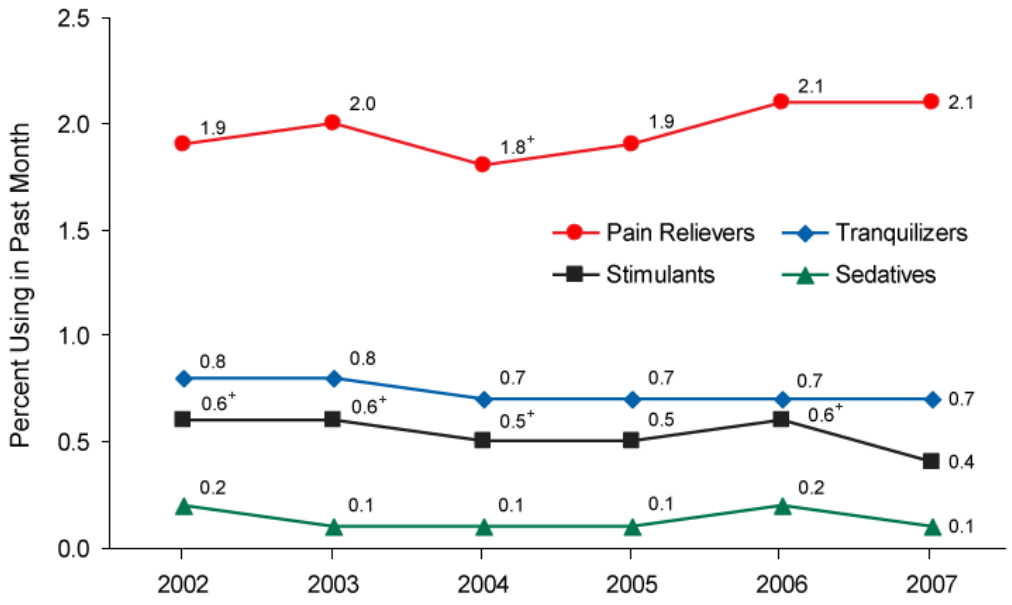
Improvements in the tamper resistance of reformulated OxyContin® is expected to reduce, if not eliminate, some of the major health risks of current OxyContin®. These improvements in reformulated OxyContin® are expected to reduce the risk of overdose and death when crushed and consumed orally, snorted, injected or used by other routes of administration. The crush resistant characteristics of reformulated OxyContin® will also be an important safety feature when misused by legitimate patients.

1 Opioid and OxyContin® abuse

Pharmaceutical opioids are vital in the control of pain for many millions of Americans, with most patients finding significant relief, with neither severe side effects nor the emergence of abuse. Nonetheless, abuse and diversion do occur and contribute to the serious problem of illicit drug use and nonmedical use of prescription drugs both domestically and internationally. The 2007 National Survey on Drug Use and Health (NSDUH) indicated there were an estimated 19.9 million Americans aged 12 or older who were current (past month) illicit drug users, meaning they had used an illicit drug during the month prior to the survey interview *(Results from the 2007 National Survey on Drug Use and Health: National Findings)*. An estimated 6.9 million persons aged 12 years and older in the United States (US) used prescription psychotherapeutics (pain relievers, tranquilizers, stimulants, and sedatives) nonmedically at least once in the past month. Of these, 5.2 million (2.1 percent of the population aged 12 years old or older) used pain relievers, the same percentage of use as in 2006 (Figure 1). The highest rate of nonmedical use of pain relievers typically occurs in young adults. In 2007, past month use of pain relievers was 2.7 percent in youths aged 12 to 17, 4.6 percent in adults aged 18 to 25, and 1.6 percent in adults aged 26 or older.

Figure 1 Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2007. Source: NSDUH 2007

(Results from the 2007 National Survey on Drug Use and Health: National Findings)



Combined NSDUH data from 2002 to 2005 (**Table 1**) indicate that 57.7 percent of persons who first used pain relievers nonmedically in the past year used hydrocodone products and 21.7 percent used oxycodone products *(National Survey on Drug Use and Health: The NSDUH Report)*. In these surveys, respondents specified that they had used hydrocodone products that included Vicodin®, Lortab®, Lorcet®/Lorcet Plus®, generic hydrocodone, and other pain relievers containing hydrocodone. Oxycodone products were reported to include Percocet®, Percodan®, Tylox®, OxyContin®, and other pain relievers containing oxycodone.

Table 1 Percentages Reporting Nonmedical Use of Hydrocodone and Oxycodone Products among Past Year Nonmedical Pain Reliever Initiates Aged 12 or Older, by Gender and Age Group: 2002-2005.

Demographic Characteristic	Hydrocodone Products		Oxycodone Products	
	Percent	SE	Percent	SE
Total	57.7	1.13	21.7	0.80
Gender				
Male	61.4	1.51	22.9	1.16
Female	54.9	1.59	20.8	1.07
Age				
12 to 17	55.4	1.10	20.3	0.87
18 to 25	64.1	1.24	27.4	1.11
26 to 34	59.5	4.58	20.3	3.47
35 to 49	54.6	5.33	14.9	3.70

Source: SAMHSA, 2002-2005 NSDUHs *(National Survey on Drug Use and Health: The NSDUH Report).*

Data on drug-related emergency department (ED) visits provide an indication of the physical harm that may result from drug misuse and abuse. According to Drug Abuse Warning Network (DAWN) data, of an estimated 106 million ED visits, there were nearly 1.3 million ED visits associated with drug abuse or misuse, of which approximately one half million involved nonmedical use of pharmaceuticals in 2004 *(The DAWN report: Emergency department visits involving nonmedical use of selected pharmaceuticals)*. Of these visits, 31.9 percent involved opiates/opioids, 29.1 percent involved benzodiazepines, and 5.7 percent involved muscle relaxants. An estimated 158,281 ED visits involved opiates/opioids. The most frequently listed opiates/opioids were hydrocodone products (26.8% of opiates/opioids), oxycodone products (23.1%), and methadone (20.1%).

OxyContin® (controlled-release oxycodone hydrochloride) is a prescription pain reliever that first became available in 1995. It is presently available in strengths of 10, 15, 20, 30, 40, 60, and 80 milligrams of oxycodone hydrochloride. Although OxyContin® accounts for a small proportion of overall pain reliever nonmedical use, this drug is of particular concern because nonmedical use has persisted despite strong efforts to reduce diversion and abuse. Lifetime nonmedical use of OxyContin® increased in the US from 1.9 to 3.1 million persons between 2002 and 2004 *(Results from the 2004 National Survey on Drug Use and Health: National Findings)* .

2 Recreational misuse and tampering practices involving opioid formulations

The prevalence of nonmedical use, or misuse, of all prescription pharmaceuticals combined now rivals that of illicit drug use in the United States. Some abusers resort to "tampering" (i.e., physical and/or chemical alteration) with pharmaceutical formulations in attempts to achieve a bigger, faster "high" (euphoric effect). Increasing the magnitude and speed of drug onset is thought to enhance the reinforcing properties of psychoactive drugs *(College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement, Reinforcing effect as a function of infusion speed in intravenous self-administration of nicotine in rhesus monkeys)*. Tampering methods that increase the dose and speed of drug delivery primarily involve chemical and physical alteration of specific pharmaceutical products. Cone *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)* provided an extensive review of methods of pharmaceutical tampering as described and discussed on the Internet. This review provided details of tampering methods practiced with numerous types of pharmaceutical products including opioids. Perceived motives for tampering by nonmedical users were cited by Cone *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)* as enhancement of psychoactive effects, enhancement of drug availability, faster onset of effects, and elimination of undesirable excipients.

Additionally, pain patients prescribed OyxContin® may inadvertently be exposed to more rapid delivery if they attempt to adjust their dosage or save money by cutting tablets into pieces. Still other patients, or their caregivers, may crush tablets and add to applesauce or other foods if they have difficulty swallowing, and some patients might chew the product unaware of the danger of such use. Although labeling warns against all tampering, this type of use by pain patients is dangerous. A formulation that reduces the risk and/or consequences of tampering could be an important step towards improving the safety profile of OxyContin® for patients.

Through design of their composition, controlled release formulations inherently retard rapid drug release. Formulations of controlled release opioids appear desirable to those engaged in misuse and tampering because of higher doses compared to immediate release products. Overcoming these controlled release mechanisms thus becomes a goal of some nonmedical users who attempt various tampering practices.

Tampering methods range from the simple to the complex. A general hierarchy of tamper assessment procedures for oral formulations (adapted from Cone *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)*) is shown as follows:

- Crushing/powdering for oral and intranasal use
- Simple hybrid methods: crushing/powdering plus extraction (may involve use of heat or filtration in some steps)
    - Crushing/powdering, extraction
        - Aqueous/alcohol extractions: single step involving use of common household solvents, e.g., water, ethanol, household products such as vinegar
            - For direct use or further steps required, e.g., concentration

        - Organic solvent extractions: single step involving use of toxic, flammable solvents, e.g., methanol, acetone, ethyl acetate
            - Solvent removal, e.g., evaporation
            - Solution or further steps required for use
- Complex hybrid methods: (may involve use of heat and/or freezing in some steps)
    - Crushing/powdering
    - Solution in aqueous/alcoholic solvents
    - pH adjustment (note: precipitation could be attempted at this point)
    - Drug extraction with organic solvents, e.g., hexane, chloroform, petroleum ether, paint thinner
        - Evaporation, solution, filtration, use, or further extraction
        - Drug extraction from organic solvent into acid solution
        - pH adjustment
        - Precipitation, solution, use, or further purification for use

Detailed instructions for tampering can be found on the Internet where many tampering methods have been reported by nonmedical users. These instructions are frequently some hybrid combination of the above methods but it appears that the most commonly used approaches by drug abusers are simple. Most nonmedical users who are attempting to abuse the drug prefer tampering methods that can be accomplished immediately with household items, e.g., crushing tablets with a spoon, rapid solution with water *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)*. More motivated abusers may attempt complex hybrid methods of tampering involving physical manipulation and extraction. Complex hybrid methods of tampering most likely would be attempted by individuals with some chemistry training and access to resources not commonly found in the household, e.g., organic solvents, acids, glassware suitable for extraction. Some key observations regarding common tampering practices from the Cone review *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)* are the following:

- Increasing the speed of drug delivery is a frequent motivation for tampering.
- Abusers are adventurous and are willing to try tampering methods that may enhance speed and magnitude of drug effects.
- Numerous methods of overcoming drug/formulation barriers have become known to abusers.
- Complex tampering procedures, even if successful, are not widely utilized by abusers.
- Drug formulations that present significant barriers to tampering reduce, but do not totally eliminate misuse or abuse.
- The Internet is a prime source of information on drug tampering and offers a broad sweep of information on methods that spans from vague to highly descriptive, inaccurate to accurate, and scattered to organized.

Tampering with a controlled release product generally involves the following elements: product knowledge, information on tampering methods applicable to the product, time for experimentation, effort, resources, and motivation. Tampering methods that involve considerable time, effort and resources are used less than simple methods that can be performed in a matter of minutes.

Conceptually, a formulation “barrier” in a controlled release product makes it more difficult to convert to a form akin to an immediate release product. Elements of formulation barriers that are considered to retard tampering include:

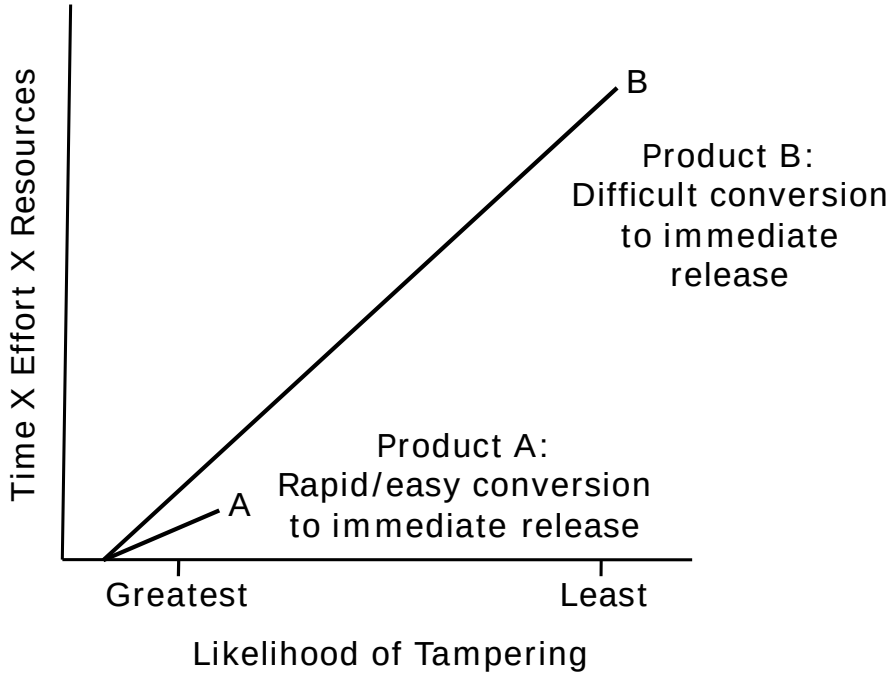
- Difficulty in crushing/powdering
- Difficulty in extraction
- Need for specialized equipment
- Need for purification efforts to recover active and eliminate excipients
- Addition of sequestered antagonists
- Addition of aversive chemicals that only become aversive when excessive doses are taken

A barrier to tampering, consequently, increases what has been referred to as the "response cost", which can be expressed as the total work (time x effort) in addition to the financial cost of the drug and any materials needed for tampering and self-administration. In general self-administration of addictive drugs follows general economic principles whereby increasing cost (expressed by effort and/or financial expenditure) decreases the rate of self-administration and reinforcing effects *(The Economic Analysis of Substance Use and Abuse: An Integration of Economic and Behavioral Economic Research)*. Laboratory evidence of these conclusions is strong: decades of studies that have examined drug dosage level and cost demonstrated that while increasing dose is associated with increased intake, increased cost decreases intake until the cost is reached at which intake ceases ("break point") *(The Economic Analysis of Substance Use and Abuse: An Integration of Economic and Behavioral Economic Research, Similarities in animal and human drug-taking behavior)*.

The functional effect of the reformulated OxyContin® technology is to substantially increase the response cost and impair the practical ability of the drug abuser to easily extract and self-administer high doses at rapid delivery rates achieved by crushing and swallowing, nasal insufflation, and intravenous injection with currently available oxycodone formulations.

The complex of requirements for tampering, when considered as a whole, can be expressed as a "barrier" in terms of time X effort X resources. A general illustration of the "barrier" concept is shown in **Figure 2** for two products. Product A (e.g., OxyContin®) is a controlled release opioid formulation that can be converted within a few seconds with simple resources, e.g., crushing with a spoon, to an immediate release form with almost all of the active ingredient made available. Product B (e.g., reformulated OxyContin®) is a controlled release opioid formulation that requires significantly more time, resources, and skill to release only a portion of the active ingredient. The introduction of a substantially higher barrier in the Product B formulation is likely to reduce the vast majority of tampering attempts with the product.

Figure 2 Illustration of the effect of formulation barriers on likelihood of tampering.



3 Tampering with OxyContin®

OxyContin® is prescribed in doses ranging from 10 to 80 mg for relief of chronic pain. When used as intended, OxyContin®'s controlled release mechanism slowly releases oxycodone over a period of 12 hours, providing safe and effective pain relief. In the late 1990s OxyContin® became a target of misuse after the realization that breaking, crushing or chewing the tablet could release oxycodone from the controlled release matrix of the tablet. With this knowledge, nonmedical users began crushing the formulation for oral use and "snorting" (intranasal use), and dissolving the powder for intravenous injection. Amongst some legitimate medical users prescribed OxyContin®, therapeutic misuse also occurred when patients mistakenly chewed or crushed the tablet for easy oral consumption, or cut the tablet in half to save money rather than swallowing the intact tablet as intended, posing a safety risk to these patients.

Overdoses and deaths from misuse of OxyContin® are well known. Individuals, including patients, who are non-tolerant to the effects of opioids are especially at risk of toxic overdose and death when taking the higher doses. Misuse of OxyContin® with other central nervous system depressants has exacerbated the problem and increased the death toll for this product *(Oxycodone involvement in drug abuse deaths. II. Evidence for toxic multiple drug-drug interactions)*.

In addition to qualitative descriptions of tampering on the Internet, demographic studies have attempted to estimate the prevalence of OxyContin® and oxycodone nonmedical use and their reported routes of administration. Carise et al. *(Prescription OxyContin abuse among patients entering addiction treatment)* evaluated the prevalence of OxyContin® use and abuse among a population of 27,816 subjects admitted to 157 addiction treatment centers in the US from 2001-2004. Approximately 5% (N=1425) reported ever using OxyContin®. Eighty-six percent (N=1208) of OxyContin® users reported using it to “get high or get a buzz”. Seventy-two percent of individuals categorized as “users” (N=1368) of OxyContin® reported their route of administration as follows:

- Oral route: 72% (N=981)
- Inhalation of crushed tablets: 11% (N=153)
- Injection of crushed tablets: 17% (N=234)

These data indicate that oral use of OxyContin® was most prevalent but did not indicate the extent to which OxyContin® is crushed or chewed for oral consumption. The authors noted that 92% (N=1242) of individuals categorized as “users” of OxyContin® reported using the medication with one or more other opioid(s) (heroin, methadone, hydromorphone, hydrocodone, and oxycodone). Only eight (0.5%) of the 1425 individuals categorized as “users” of OxyContin® reported no use of any additional drugs other than alcohol.

A study by Davis and Johnson *(Prescription opioid use, misuse, and diversion among street drug users in New York City)* of prescription opioid use, misuse and diversion among 586 street drug users in New York City identified 192 individuals who had used OxyContin®. Injection of OxyContin® was rarely reported (N=7, 3.6%), whereas snorting/sniffing was more prevalent (N=43, 22.4%).

A 2009 review of Purdue Pharma L.P.'s worldwide safety database identified a total of 1,396 oxycodone controlled release (CR) cases that described overdose, intentional drug misuse, medication error, and/or drug abuse associated with the tampering of an oxycodone CR tablet *(Reports of Tampering with OxyContin® Tablets: Postmarketing Experience (February 2009))*. The majority of the cases originated in the U.S. (N=1,346) and involved reports of drug abuse. Reports involving drug administration errors / medication errors accounted for less than 15% of the cases. The majority of the cases identified involved adults (18 years of age and older) and described crushing OxyContin® tablets for the purposes of snorting, injecting (intravenously) and / or smoking the crushed tablet (listed in descending order of frequency). One hundred and eighty two (182) of the 1,346 cases involved "chewing" OxyContin® tablets. Of these 182 cases, 125 involved reports of drug abuse. The remaining 57 cases involved medication errors or accidental exposures. Twenty two (22) of the 182 cases were associated with a fatal outcome. One hundred and three (103) cases involved adolescents (13 to < 18 years). All of the adolescent cases were associated with drug abuse, with the most common route of abuse being intranasal inhalation (snorting) in 71 of the 103 cases. Nineteen (19) of the adolescent cases were associated with a fatal outcome. Eighteen (18) cases involved "children." Thirteen (13) of the 18 children were 6 years of age or younger. Ten (10) of these 13 cases involved "chewing" an OxyContin® tablet. Two of the cases involved children of unspecified age who "chewed up" OxyContin® and died. The case outcomes for the other reports were unknown.

Internet-based estimates of prevalence of drug abuse practices have limitations that have been described elsewhere *(Ephemeral profiles of prescription drug and*

formulation tampering: Evolving pseudoscience on the Internet) but Internet-based surveys can provide information for understanding patterns and trends of drug abuse. An Internet-based survey (N=896) of nonmedical prescription opioid use in the US by Katz et al. *(Internet-based survey of nonmedical prescription opioid use in the United States)* revealed that 188 individuals had used OxyContin® nonmedically. Routes of administration reported by the 188 OxyContin® users were as follows: swallow (without chewing) (N=104, 55.5%); chew (N=64, 34.0%); snort/sniff (N=140, 74.5%); smoke (N=20, 10.6%); inject skin (N=10, 5.3%); inject vein (N=30, 16.0%); and other (N=2, 1.1%). (Note: Some individuals reported nonmedical use via multiple routes of administration, thus the total percentage exceeds 100%).

A recent survey of Erowid.org, one of the leading Internet sites that posts drug abuse experiences reported by drug abusers, provided information on tampering methods employed by OxyContin® abusers. The survey was performed of Erowid Experience Reports (accessed February, 2009) (http://www.erowid.org/experiences/exp_search.cgi) for oxycodone (only). The results of the survey provided a current "snapshot" of methods of abuse and tampering with oxycodone and OxyContin® products. The site search provided a listing of 89 reports from individuals who had used oxycodone. Individual reports from this site, in many cases, identified the oxycodone product, route(s) of administration, and in some cases, details of tampering methods that were employed. Of the 89 reports, 86 (96.6%) involved abuse while 3 (3.4%) were probable therapeutic use. Eighty-two percent of the reports identified at least one oxycodone product by name. Many of the reports identified the route(s) of administration. A summary of the routes of administration for the 86 abuse reports is shown in **Table 2**.

Table 2 Summary of Internet Survey of Reports on Erowid.Org (Experience Reports) on Abuse of OxyContin® and Other Oxycodone Products by Reported Routes of Administration (reports were accessed February, 2009)

Product	N	%Total	Oral - intact	Oral - chew	Oral - drink	Oral - cut/crushed	Oral - parachute	Intranasal	Injection	Smoke	Rectal
OxyContin®	51	59.3	11	8	1	4	1	39	6	0	1
Percocet®	12	14.0	9	4	0	0	1	2	0	1	1
Tylax®	1	1.2	0	0	1	0	0	0	0	0	0
Oxycet®	1	1.2	1	0	0	0	0	0	0	0	0
Endocet®	2	2.3	2	0	0	0	0	0	0	0	0
Roxicet®	2	2.3	1	0	0	0	0	1	0	0	0
Roxicodone®*	1	1.2	0	1	0	0	0	0	0	0	0
Unidentified	16	18.6	9	0	0	0	0	8	1	1	0
Total	86	100	33	13	2	4	2	50	7	2	2
%			38.4	15.1	2.3	4.7	2.3	58.1	8.1	2.3	2.3

Of the 51 reports of abuse of OxyContin®, intranasal (snort/sniff/insufflate) administration (N=39, 76.5%) was the most frequently described route, followed by oral (intact) (N=11, 21.6%), oral (chew) (N=8, 15.7%), injection (N=6, 11.8%), and oral (crushed) (N=4, 7.8%). There were mentions in single reports (N=1, 2.0%) of oral (drink), oral (parachute), and rectal ("plugging") administrations. Numerous methods of cutting and crushing OxyContin® and oxycodone tablets were described in these reports including use of a hammer, pill cutter, credit card, key, and pocket knife. Such detailed descriptions are invaluable in developing protocols to assess the ability of new formulations to resist real world tampering approaches.

The percent of posts on Erowid mentioning each route of administration is quite different than what has been reported for patients entering treatment programs (Prescription OxyContin abuse among patients entering addiction treatment), indicating that this may be a unique group of misusers/abusers. A prototypic example from the Erowid reports illustrates the level of detail that is often presented. One individual (Report 4, Appendix 1: Summary of Erowid.com User Experience Reports on Oxycodone) described crushing an OxyContin® tablet as, "I proceed to pound … with a hammer, leaving me

with a baggy full of white powder…" for use by insufflation. Another individual reported crushing oxycodone (unspecified product) in the following manner, "With a hammer I gently tapped each pill, causing it to crumble into smaller pieces. I then pressed the head of the hammer onto the pile of pieces and applied a gently rolling pressure so as not to lose any precious powder. With relative ease the pile of pills was transformed into a very fine mountain of powder". Another individual described preparation of OxyContin® for injection as, "He broke my 80mg tablet of Oxy into 4 similar pieces and placed them into a spoon. He then pulled 85 units of clean water into my syringe, and squirted it onto the pill. Next, he cooked the pill with a Bic until there was some bubbling and a faint trace of steam above the mix. In one motion, he crushed the cooked pill with the back of the plunger, and it squished down into the mix. Last, he placed a tic-tac sized cotton piece in the spoon, and drew up roughly 70 units of liquid oxycodone into the syringe". This same report also described the method of injection as, "I tied my right arm off with my belt, pulled it tight with my teeth, and let him spot the vein. He inserted the needle head, pulled back blood to indicate a clean vein hit, and pushed the plunger down as I let loose the tie". The effect of this injection was described as "INSTANTLY, I felt my first real head rush, and let me tell you, it was insane. All at once, the tension in my body released, and I fell back onto a pillow, and stared at the ceiling, enjoying the incredible wave of warmth that surrounded my being. It was as if God himself reached through the clouds and granted me total bliss, without any responsibilities or worries. The world was suddenly right, and all of the suffering of humans no longer mattered. I distinctly remember it as the most euphoric moment of my life".

Although there appears to be wide variability in patterns of tampering and misuse (as inferred from reported routes of administration) among different populations, the above studies and surveys suggest a pattern of tampering and nonmedical use with OxyContin® as follows: swallowing with/without chewing/crushing ≈ intranasal > injection >> smoking ≈ rectal.

4 New Oxycodone Controlled Release Formulation

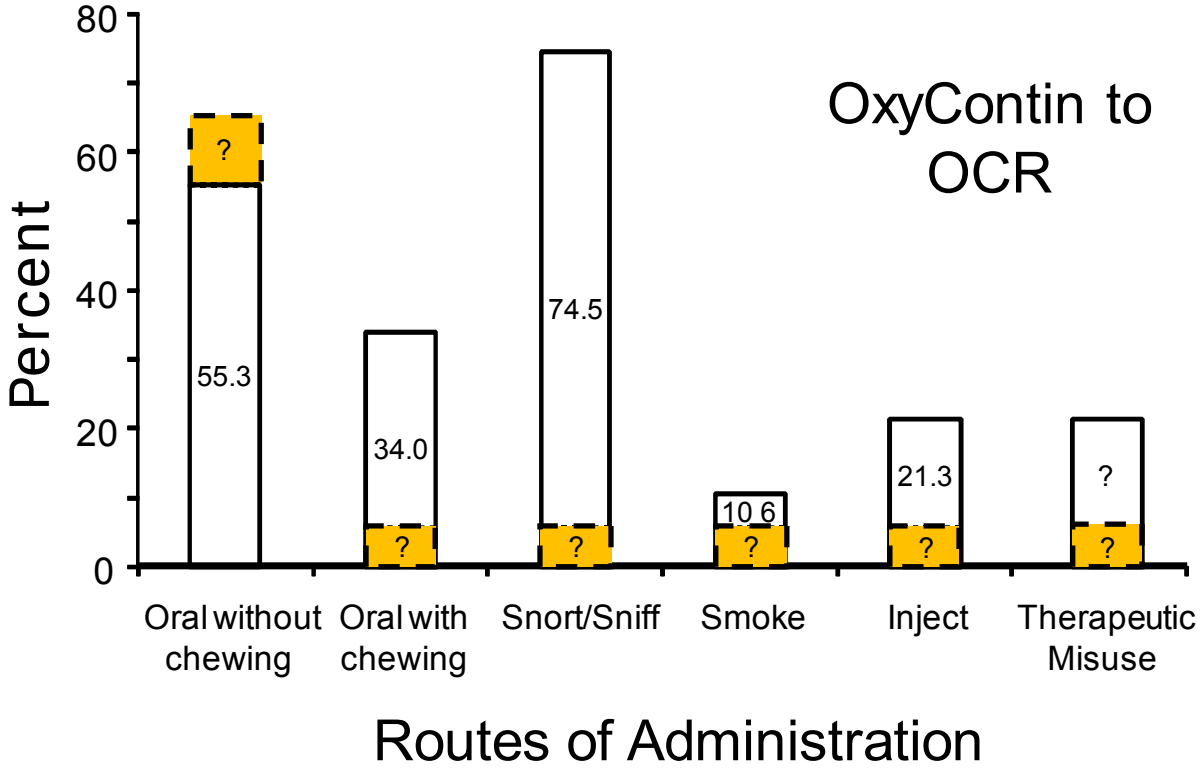
Purdue Pharma has developed a reformulation of OxyContin® that will replace all current strengths of the current product. Reformulated OxyContin® incorporates new technology that provides the following improvements in tamper resistance:

- Crush resistance
- Forms a (b) (4) when placed in (b) (4) or other solvent
- Reduced active pharmaceutical ingredient (API) release in water, alcohol and other common solvents compared to OxyContin® treated similarly

These properties were incorporated into reformulated OxyContin® with the intent to improve safety and to reduce/eliminate the most commonly employed methods of tampering (formulation alterations) with current OxyContin®. The combination of these properties is expected to introduce a significant barrier to tampering with OxyContin® and substantially reduce efforts to alter the formulation for enhanced effects by the oral route (chewing/crushing), intranasal route (snorting), parenteral use (injection), and smoking. **Figure 3** illustrates this concept for current OxyContin®, which is a controlled release formulation that is easily converted by crushing to an immediate release product. The data on prevalence of route of administration of current OxyContin® is adapted from Katz et al. *(Internet-based survey of nonmedical prescription opioid use in the United States)*. The shaded bars represent the direction of the expected prevalence of abuse when reformulated OxyContin® replaces current OxyContin®. Other than abuse of the reformulation by swallowing intact (which may increase as a result of the difficulty experienced in attempted tampering efforts), tampering efforts involving chewing, crushing and extraction are expected to be substantially reduced or eliminated. Although prevalence is not known, it should be noted that therapeutic misuse (e.g., pain patient who cuts or crushes a tablet rather than swallowing intact) is a current safety risk that also should be reduced or eliminated.

Figure 3 Expected Effect of Replacement of current OxyContin® with reformulated OxyContin® on Prevalence Rates of Tampering For Oral Use and Other Routes of Administration.

Data are adapted from Katz et al. *(Internet-based survey of nonmedical prescription opioid use in the United States).* Shaded bars indicate the predicted direction of change in prevalence rate.



5 General Principles in Assessment of Tamper Deterrent Formulations

Designing validated laboratory methods for tamper assessment of the reformulation presents a challenge as no current standards have been established for tamper assessment of controlled release oral formulations. Protocols for tamper assessment must be developed based on known and potential methods that are considered likely to be practiced by misusers and abusers.

Assessment of tamper deterrent formulations must take into consideration the chemical nature of the opioid active and of other actives (if present), and the physical and chemical features of the formulation as a whole. The intended therapeutic route of administration is also a key consideration in assessing tamper deterrent formulations. Products designed for different routes of administration, (e.g., oral, transdermal, sublingual), require somewhat different considerations and different assessment approaches.

In the case of oral misuse, the first consideration is the ability to chew/cut/powder the product with the resulting effect of these manipulations on drug release rate. Powdering a formulation for oral administration is quite commonly reported by individuals engaged in abuse of opioids. Powdering enables “parachuting” (e.g. encapsulation of powder in tissue paper and swallowing), and also allows the possibility of intranasal (snorting/sniffing) route, the second most common route of abuse. Further efforts including simple or complex extractions are required for use by injection routes. The smoked and rectal route for opioids should also be considered as possible alternative routes for some abusers, but these routes appears to be utilized with substantial less frequency than oral, intranasal, and intravenous use.

The simplest means of tampering is most desirable to abusers. A brief hierarchy of tamper assessment procedures follows the order (simple to difficult):

- Crushing/powdering
- Extraction: Single step
    - Common household solvents, e.g., (b) (4) ((b) (4)
    - Organic solvents, e.g., (b) (4)
- Extraction/precipitation

- Extraction: Multi-step:
  - complex procedures o (b) (4) with (b) (4) into (b) (4) and further isolation steps (e.g. (b) (4) (b) (4) (b) (4)

Protocols for assessment of the "crushability" of a formulation should address the following:

- Ease of crushing/powdering
- Resource requirements
- Particle size distribution
- Extraction and dissolution characteristics of powder versus intact formulation
  - Effect of crushing on dissolution (rate of release over time)

Protocols for assessment of the "extractability" of reformulations should address the following:

- Resource requirements
- Time requirements
- Chemical training/knowledge requirements
- Hazard risks
- Toxicity risks
- Suitability for oral, intranasal, intravenous, and smoked administration

Protocols for assessment of the ability of a reformulation to be vaporized (smoked) should address the following:

- Resource requirements
- Time requirements
- Heat source and conditions
- Form of active (b) (4)

Suitable assays for drug measurement that are capable of specific and sensitive measurement of active drug (e.g., HPLC or other methods) should be utilized. All analytical methods must be validated and procedures should be conducted under blind conditions (to the extent possible). Use of independent laboratories that follow good laboratory practices to conduct tamper assessment protocols adds additional credibility to the results. Analytical results of all tamper assessment procedures should be reported in terms of extraction efficiency, recovery of active (percent dose), absolute amount of active recovered (mg), and purity (to the extent possible, dependent upon procedure).

6 Development of tamper assessment protocols for *in vitro* testing of reformulated OxyContin

The development of *in vitro* laboratory methods for tamper assessment of reformulated OxyContin® involved consideration of the following questions:

- What are the most common methods employed in tampering with OxyContin®?
- What are the most common routes of administration likely used by abusers of OxyContin®?
- What methods of inadvertent tampering are most commonly used by legitimate users that may result in overdose?
- What are the physico-chemical differences between OxyContin® and reformulated OxyContin®?
- What new and existing methods of tampering are most likely to be attempted with reformulated OxyContin®?

These questions were addressed by a) reviewing the scientific literature on methods of tampering with OxyContin® and other opioid formulations, b) reviewing the scientific literature on common routes of administration of oxycodone by misusers and abusers, c) reviewing Internet reports on tampering with oxycodone, d) input from an external

Expert Panel experienced in drug abuse treatment and tampering methods, and e) input from experienced individuals who are knowledgeable about extraction techniques suitable for purification of oxycodone from complex matrices and excipients. This information was used to develop a comprehensive series of laboratory-based *in vitro* assessment protocols for evaluation of the "tamper resistant" properties of reformulated OxyContin®. The experimental design of each protocol included the following elements considered necessary to yield reliable scientific data:

- Testing of all dose strengths of reformulated OxyContin®
- Testing methods extended to determine failure limits
- Inclusion of adequate controls for comparison to current OxyContin®
- Sufficient replicates for evaluation of method variability
- Method validation procedures
- Investigation of a range of conditions on outcome of results, e.g., temperature, time
- Use of independent laboratories
- Testing under blind conditions to the extent possible

The scope of these protocols covered commonly known methods of tampering with oral opioid formulations (OxyContin®, oxycodone and other opioids) as well as methods that were considered likely to be attempted by experienced tamperers. Each protocol was developed to address at least one method or component of common tampering attempts currently employed or predicted to be employed with reformulated OxyContin®. Specifically, *in vitro* tests were designed to provide an accurate assessment of the potential for reformulated OxyContin® to be tampered with for the following types of misuse:

a. Crushability: chewing, cutting, grinding, powdering

b. Swallowing: chewed or powder (dissolution)

c. Effect of co-consumption of alcohol on “dose dumping”

d. Extraction (simple and complex methods)

e. Injection (syringeability and injectability)

f. Nasal insufflation (snorting/sniffing)

g. Smoking

h. Rectal (“plugging”)

i. (b) (4) isolation (for use by different routes of administration)

a. Crushability: chewing, cutting, grinding, powdering

Chewing and crushing current OxyContin® are the most common means of tampering. This approach to tampering converts OxyContin® into a (b) (4) controlled release properties of OxyContin®, with the dosage form readily available for immediate use. In this form powdered OxyContin® can be used readily by the intranasal route (snorting/sniffing) as well. Further, powdering is the first step in simple and complex extraction methods employed by injection users or by smokers of the product. Hence, assessment methods were devised to assess the difficulty of the “crushability” of reformulated OxyContin®.

Starting with the knowledge that current OxyContin® can be easily chewed or crushed in a few seconds with a (b) (4) or spoon, the potential that reformulated OxyContin® could be crushed with readily available equipment required systematic evaluation. Initial exploration of tampering methods was performed by Purdue Pharma to determine which methods would prove most successful. With input from outside experts, early evaluations included attempts at crushing reformulated OxyContin® with a variety of

(b) (4) tools (e.g., (b) (4), (b) (4) The (b) (4) produced various deformations of the tablet, but most were not successful in producing a (b) (4) powder. Electrically powered (b) (4) and (b) (4) were most effective in (b) (4) reformulated OxyContin®. Additional studies were performed to determine the effects of time (how long was needed to reach (b) (4) particle size (b) (4)?) and temperature (b) (4) (b) (4)?) on powdering reformulated OxyContin®.

(b) (4)

All methods, aside from (b) (4)g and use of (b) (4), produced a spread of particle sizes ranging from (b) (4)) to (b) (4)). Thus, qualitatively, it was established that reformulated OxyContin® could be reduced to varying particles sizes by use of diverse (b) (4)instruments. However, extreme variability in particle size production was clearly evident in all methods. This variability in particle size depended upon the specific instrument used and the time and effort expended.

In general, all methods, with the exception of whole, deformed tablets, produced a (b) (4) of particle sizes. A systematic approach was needed to overcome the extreme

variability in production of different particle sizes found with different methods and different conditions. Consequently, particle size (b) (4) selected for use in *in vitro* assessment protocols. (b) (4) (b) (4). Results of these studies on crushability are described in the Study 1 section of the main body of the **Briefing Document**.

b. Swallowing: chewed or powder (dissolution)

Chewing and oral consumption of powder, e.g., "parachuting" of OxyContin® is the most common means of tampering for abuse. *In vitro* studies were designed to determine if powdered reformulated OxyContin® would retain controlled release properties of the intact tablet. Dissolution experiments were designed to compare rate and extent of release of oxycodone over time in (b) (4)). Results of the studies on dissolution are described in the section of the main **Briefing Document** on Study 3.

c. Effect of co-consumption of alcohol on "dose dumping"

The concern that co-consumption of alcohol with intact reformulated OxyContin or powdered reformulated OxyContin® would result in rapid release of oxycodone was assessed in *in vitro* dissolution experiments. Tests were conducted with 1)(b) (4), and 2) (b) (4) in which the alcohol content was (b) (4) Results of the studies on dissolution in alcohol are described are also described in the section of the main **Briefing Document** on Study 3.

d. Extraction (simple and complex methods)

A series of simple to complex extraction protocols were designed to cover a range of known and predicted methods of tampering with reformulated OxyContin®. These protocols incorporated common practices reported on the Internet by abusers who describe methods used to purify and concentrate oxycodone and other opioids from various formulations.

Simple extraction methods are generally employed for injection. The first step in such a process requires crushing an oxycodone tablet followed by (b) (4) in a suitable (b) (4) media. If the solution step, e.g., (b) (4) (b) (4)r, is not successful in producing a solution suitable for injection, some abusers will resort to more elaborate means of extraction.

Simple step extractions protocols were developed to address the difficulty of extraction, primarily with the intent of producing an extract that could be injected or used by other routes of administration. The following types of extraction protocols were developed to assess relatively simple extraction methods reported or predicted to be employed by opioid tamperers. The methods are generally ranked in order of difficulty (simple to complex):

It should be noted that extractions involving organic solvents other than ethanol are not suitable for (b) (4) and require additional purification efforts and treatments, (b) (4).

A substantially smaller number of individuals who are highly motivated and have the necessary knowledge (information, skills, training), resources, and adequate drug supply, may resort to more complex purification schemes. The most difficult extraction conditions often involve methods similar to those employed in laboratory methods for purification of oxycodone. Complex tampering methods typically involve multiple steps including the following: (b) (4) (b) (4) Further effort is then required to convert the (b) (4) into a usable form for drug administration.

A complex extraction protocol was developed along these lines to assess the efficiency of , some the most commonly utilized (b) (4) solvents encountered in Internet tampering recipes for opioids. The protocol incorporated (b) (4) maximal extraction efficiency, as frequently advised in Internet recipes.

Results of the studies on extraction are described in the main body of the **Briefing Document** in the sections on Study 2 and Study 4.

e. Injection (syringeability and injectability)

Because reformulated OxyContin® produces a (b) (4) in (b) (4) (b) (4)r, no solution is available for injection when performed, as commonly reported for current OxyContin®, i.e., crushing, solution in (b) (4) in a spoon, and heating. It is feasible that some individuals attempting to produce a solution of oxycodone from

reformulated OxyContin® for injection will attempt use of larger volumes of water for preparation of injection solutions.

In prior experiments (b) (4), (b) (4), powdered reformulated OxyContin® immediately forms a (b) (4) and is virtually impossible to syringe. To identify the conditions in which powdered reformulated OxyContin® could be used for intravenous injection, two protocols were designed to assess whether finely powdered reformulated OxyContin® dissolved (b) (4) (b) (4) could be drawn into a syringe with a needle (syringeability) or expelled (when loaded into the barrel) from a syringe with a needle. Although injection (b) (4) is considered unlikely to be practiced by injectors, these conditions were chosen to represent the extremes in volume that some abusers might attempt to use.

The syringeability protocol was designed to determine if (and how much) finely powdered reformulated OxyContin® when mixed with (b) (4) at either (b) (4) or and followed by could be drawn into a syringe fitted with a needle. Needle sizes were varied from), the latter being most representative of what is used by injectors. (b) (4) (b) (4) are the most common type used by abusers.

The injectability protocol was designed to determine if (and how much) finely powdered reformulated OxyContin® when mixed with (b) (4)r at either (b) (4) temperature or (b) (4) to (b) (4) and loaded into the open barrel of the syringe could be expelled from the syringe through a needle. Needle sizes were varied from (b) (4) (b) (4)

Results of the studies on syringeability and injectability are described in the main body of the **Briefing Document** in the sections on Study 5.

f. Nasal insufflation (snorting/sniffing)

Consideration of the physiology of the nose is important in assessing whether powdered reformulated OxyContin® is likely to be administered by the intranasal route. The nose is extremely efficient in preventing particles with a size larger than 10 μm from reaching the lungs. The high linear velocity and the bend in the airstream in the anterior nares results in impaction of a large proportion of particles that enter the nasal airway. Insoluble particles deposited in the main nasal passage are transported by mucociliary clearance to the back of the throat and swallowed. If the particle is soluble, it may readily pass into the mucosa and then be absorbed into the bloodstream. The absorption of low molecular weight drugs by the nasal mucosa appears to be primarily dependent upon diffusion processes. Consequently, absorption will be highly dependent upon drug concentration in solution, surface area, and contact time between drug and the mucosal tissue. The following drug factors appear to be important to the bioavailability of intranasal administered drugs:

- Absorption mechanisms
- Drug concentration
- Dispersion of the drug in the nasal cavity
- Contact time of drug with nasal mucosa
- Dissolution time
- Viscosity of the drug solution

Generally, snorting OxyContin® is the most frequent alternate route of administration reported by abusers *(Internet-based survey of nonmedical prescription opioid use in the United States, Prescription opioid use, misuse, and diversion among street drug users in New York City)*. However, this may be the least dangerous route of administration,

given inherent limitations on the magnitude of dosing and frequency of use, when compared to oral and intravenous administration *(Drugs and Chemicals of Concern: Oxycodone: Summary of Medical Examiner Reports on Oxycodone-Related Deaths)*. The popularity of the snorting route undoubtedly resides in the simple preparation steps involved, e.g., crushing, and the rapid onset of reported effects relative to oral administration.

Snorting OxyContin® requires crushing the tablet to a fine powder as a starting point followed by inhaling powder into the nose. Absorption of intranasally administered oxycodone by the nasal mucosa requires dissolution of the product in biofluid present in the nasal mucosa. The pH of nasal secretions ranges from 5.5 to 6.5 in normal adults. The speed of oxycodone dissolution in nasal biofluids is expected to be critical to absorption. Absorption of oxycodone by the nasal epithelium will be limited by mucociliary clearance of insoluble particles to the back of the throat where it is swallowed. Formation of a viscous gel by polyethylene oxides in reformulated OxyContin® may prolong contact time with the nasal mucosa, and thus, enhance absorption. At the same time, it is expected that gel formation will produce unpleasant sensory effects and serve as a detriment to intranasal use. For example, Internet users who attempt to snort Concerta®, a controlled release formulation of methylphenidate that contains polyethylene oxide, report that "when crushed up and snorted has been known to completely clog up the nostrils as it turns into a slime" (http://www.bluelight.ru/vb/archive/index.php/t-304858.html).

Assessment of the potential of reformulated OxyContin® use by the intranasal route can be made from the protocols that characterize the following elements essential to drug absorption from the nasal mucosa:

- Crushability, grinding and powdering potential
- Rate of dissolution
- Extraction studies in small volumes of aqueous and acidic solvents

Results of the studies on crushing, dissolution, and extraction are described in the main body of the **Briefing Document** in the sections on Study 1, Study 2, Study 2 and Study 4.

g. Smoking

Smoking is a well-known form of drug administration, but is infrequently practiced with oxycodone. Internet accounts of smoking attempts with OxyContin® tend to follow the pattern generally described for opium and heroin, e.g., “chasing the dragon” (inhaling vapors produced by heating drug on foil). The conditions for smoked OxyContin® generally include (b) (4) followed by (b) (4) the (b) (4) with application of (b) (4) the underside. The heat melts and (b) (4). Abusers attempt to inhale the (b) (4) or other (b) (4). Frequently, abusers report highly unpleasant tastes and few recommend smoking oxycodone as a means of getting “high”.

A protocol was designed for the assessment of the smoking potential of reformulated OxyContin®. The conditions were adopted to simulate application of intense heat to finely powdered reformulated OxyContin®. The laboratory device allowed air to pass over the heated reformulated OxyContin® (b) (4) and the (b) (4) collected by means of a (b) (4). Initial experiments were performed to determine the optimal temperature for vaporization of reformulated OxyContin®. Results of the studies on smoking potential are described in the main body of the **Briefing Document** in the sections on Study 5.

h. Rectal (“plugging”)

Rectal administration is infrequently reported as a means of administration of OxyContin®. The method generally involves a (b) (4) extraction of oxycodone, followed by loading into a syringe, and insertion into the rectum for administration.

Assessment of the potential for rectal abuse of reformulated OxyContin® can be made from the protocols that characterize the following elements essential to drug absorption from the rectum:

- Crushability, grinding and powdering potential
- Extraction studies in (b) (4) solvents

Results of the studies on the potential for rectal use are described are described in the main body of the **Briefing Document** in the sections on Study 1, Study 2 and Study 4

i. isolation (for use by different routes of administration)

Tampering methods reported for OxyContin® that involve routes other than oral or intranasal administration generally begin with crushing the tablet with subsequent extraction steps intended to produce concentrated solutions or residues of purified oxycodone. The motivation for many abusers, as reported on the Internet, in attempting isolation methods is not only to change the route of administration, but also to eliminate various excipients in the formulation which many abusers view as potentially harmful if used orally or injected or smoked.

Discovery of simple isolation methods that would allow recovery of relative pure drug from a formulation could result in broader tampering practices and use by additional routes of administration, somewhat akin to the “crack” cocaine epidemic. The discovery of a simple means of conversion of cocaine hydrochloride powder into “freebase”

cocaine was a significant factor in the spread of smoked cocaine abuse. The preparation of “crack” cocaine involves dissolution of cocaine hydrochloride in water and addition of a base. With cooling, insoluble cocaine base precipitates and forms “rocks” of “crack” cocaine. Another isolation procedure commonly reported on the Internet is the “cold water extraction” technique for the separation of codeine from acetaminophen *(Ephemeral profiles of prescription drug and formulation tampering: Evolving pseudoscience on the Internet)*. The codeine preparation is dissolved in water then chilled to precipitate insoluble acetaminophen. Filtration allows separation of codeine solution in a relatively pure form leaving insoluble acetaminophen and other excipients on the filter paper.

Results of the studies on isolation and purification are described in the main body of the **Briefing Document** in the sections on Study 6 and Study 7.

7 Safety benefits of reformulated versus current OxyContin®

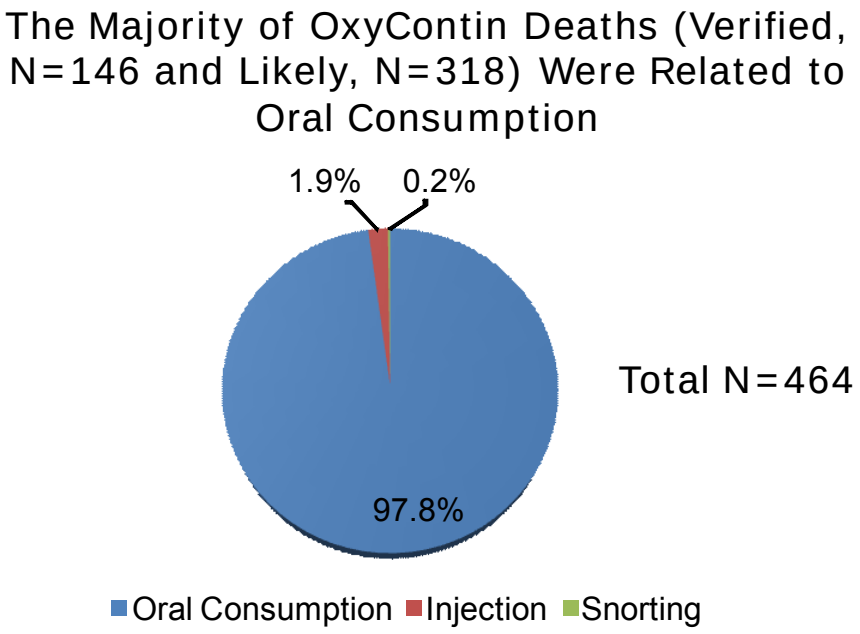
The current OxyContin® formulation can be readily converted from a safe and efficacious product when used medically as intended to an immediate release product when chewed, cut, crushed or powdered. This transformation of OxyContin® can be accomplished simply in a matter of seconds. Patients who are administered crushed

OxyContin® and abusers who knowingly tamper with OxyContin® are at risk of toxic overdose and death, especially for individuals who are nontolerant to the effects of opioids.

Numerous deaths have resulted from the use, misuse, and abuse of OxyContin®. It appears that the primary route of administration in most deaths results from oral consumption. A report by the Drug Enforcement Administration (DEA) details oxycodone-related deaths over the period 2000 and 2001 from 775 medical examiners *(Drugs and Chemicals of Concern: Oxycodone**:** Summary of Medical Examiner Reports on Oxycodone-Related Deaths).* Of the 949 oxycodone-related deaths reported to the DEA as of February 14, 2002, OxyContin® was the verified cause in 15% of cases or the likely cause of death in 34% of cases. Of the 464 deaths (49%) linked, or most likely linked, to OxyContin®, only nine (9) deaths were associated with the presence of a "recent injection site", and only one death was associated with snorting the drug. DEA concluded that the vast majority of deaths were associated with oral consumption of the drug **(Figure 4)**.

Figure 4 Routes of OxyContin® Administration Associated with Deaths Reported to the United States Drug Enforcement Agency.

(Drugs and Chemicals of Concern: Oxycodone: Summary of Medical Examiner Reports on Oxycodone-Related Deaths).



Source: Adapted from U.S. Department of Justice, Drug Enforcement Administration (DEA). "Drugs and Chemicals of Concern: Summary of Medical Examiner Reports on Oxycodone-Related Deaths," http://www.deadiversion.usdoj.gov/drugs_concern/oxycodone/oxycontin7.htm. Accessed February 1, 2009.

Improvements in the tamper resistance of reformulated OxyContin® is expected to reduce, if not eliminate, some of the major health risks of current OxyContin®. These improvements include crush resistance, formation of viscous gels upon hydration, and reduced drug release in water, alcohol and other common solvents. Even when reformulated OxyContin® is successfully crushed, it retains a major portion of its controlled release properties. These improvements in reformulated OxyContin® are expected to reduce the risk of overdose and death when crushed and consumed orally, snorted, injected or used by other routes of administration. The crush resistant characteristics of reformulated OxyContin® will be an important safety feature for patients who may want to cut the tablet to save money, inadvertently chew it, or crush and add to applesauce to make it easier to swallow. In addition, these same

characteristics will make it more difficult for someone who is attempting to abuse reformulated OxyContin® by extracting the active ingredient to use as a bolus.

8 Summary

The evaluation of tamper resistance properties of a reformulation of OxyContin® required a full assessment of the strengths and weaknesses of the product. *In vitro* assessment methods were developed that broadly captured methods that are currently employed or predicted to be employed by abusers who seek to convert the product to an immediate release form. The current formulation of OxyContin® can be easily and quickly converted within seconds to an immediate release form by cutting or crushing the tablet. Reformulated OxyContin® has added crush resistance that could deter tampering efforts, but highly motivated individuals may resort to more elaborate attempts to remove and purify oxycodone from its matrix.

The development of tamper assessment protocols for the evaluation of reformulated OxyContin® involved substantial input from experts who are knowledgeable in the wide range of chemical and physical manipulation methods that abusers use. The emphasis in the design of these protocols for tamper assessment considered the range of possibilities that extended beyond current tampering practices with OxyContin®. Experts provided input not only on known methods of tampering with OxyContin®, but considered many other ways that an opioid formulation could potentially be altered.

All protocols were designed to push the limits of experimental conditions to failure by incorporating a broad range of (b) (4). Each protocol was designed to simulate components of tampering that are practiced or could be practiced by misusers in various environments (home, parties, etc). At the same time, each protocol was designed to meet the highest standards of scientific scrutiny. Analytical methods were standardized and validated. Multiple replicates of

each test were considered necessary to assess inherent variability of each process. All dose strengths of reformulated OxyContin® were evaluated and multiple controls were incorporated into each assessment. Independent laboratories performed the assessments under blind conditions to the extent possible.

The results of these assessments of reformulated OxyContin® provide detailed, valid scientific data on the strengths and weaknesses of the reformulation when subjected to current and potential future tampering attempts across a broad range of conditions.

No formulation that still allows the drug to be used therapeutically will prevent all methods of tampering that may lead to abuse. The most important aspects of these formulations are to 1) increase the safety of the product when misused by legitimate patients and 2) to make it more difficult and time consuming for abusers to extract the active ingredient to use for immediate effect. I believe that the data support these goals for reformulated OxyContin®.

Glossary of Abuse-Related Terms

(Adapted from PinneyAssociates' definitions)

Abuse: The use of a drug in a manner detrimental to the individual or society but not meeting criteria for addiction.

Note: Abuse is sometimes used as a synonym for drug abuse, substance abuse, drug addiction, chemical dependency, and substance dependency.

Addiction: Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Note: Addiction is the more widely used term for what the American Psychiatric Association (APA) and World Health Organization (WHO) refer to in their technical and diagnostic documents as "dependence."

Diversion: The removal of legitimately-manufactured controlled medications from lawful, legitimate use into illicit drug trafficking.

Note: Diversion cases involve, but are not limited to, physicians who sell prescriptions to drug dealers or abusers; pharmacists who falsify records and subsequently sell the medications; employees who steal from inventory; executives who falsify orders to cover illicit sales; prescription forgers; and individuals who commit armed robbery of pharmacies and drug distributors.

Formulation Barrier: The response cost (time, effort, resources) required to alter a prescription medication for purposes of misuse or abuse.

Misuse: The exposure resulting from the use of a prescription medication in ways other than how it was prescribed, contrary to approved labeling unless taken as directed by a healthcare provider, and below the threshold of abuse.

Nonmedical use: The use of a prescription medication in a manner inconsistent with accepted medical practice contrary to approved labeling.

Physical dependence: Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of drug and/or administration of an antagonist and is relieved by the readministration of the drug or another drug of the same pharmacologic class.

Tampering: Chemical and/or physical alteration of a prescription medication contrary to approved labeling.

Tolerance: Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. A need for markedly increased amounts of the drug to achieve intoxication or desired effects, or markedly diminished effects with continued use of the same amount of the drug.

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