

An iterative model for *in vitro* laboratory assessment of tamper deterrent formulations

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ABSTRACT

Background: In an effort to address the continuing problem of prescription opioid abuse, manufacturers are incorporating new technologies into formulations that are designed to deter product tampering and misuse. Standards for laboratory assessment of tamper deterrent properties of new formulations have not previously been developed.

Methods: Experimental designs were developed for the *in vitro* laboratory assessment of the tamper deterrent properties of reformulated oxycodone. Given that an exhaustive study of all potential tampering methods was impractical; this model was developed to evaluate the product in an incremental fashion with iterative changes that were amenable to objective and replicable laboratory testing.

Results: A description of the model is provided along with pertinent examples involving assessment of reformulated oxycodone with comparisons to the original formulation. Physical and chemical procedures were developed that relate to “real-world” scenarios that may be applied to opioid formulations. Test results were interpreted in relation to the relative ease or difficulty of the manipulation as compared to control materials and the amount and purity of active drug that could be accessed. Results from some of the tests were designed to be useful in predicting whether specific tampering methods would facilitate or deter drug administration by different routes of administration.

Conclusions: This model, developed to assess the tamper deterrent properties of reformulated oxycodone, should have application in the assessment of other drug formulations designed to exhibit tamper deterrence properties.

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1. Introduction

Recently, the Institute of Medicine of the National Academies of Science reported that chronic pain affects an estimated 100 million American adults and costs up to \$635 billion each year in medical treatment and lost productivity (Committee on Advancing Pain Research Care and Education Board on Health Sciences Policy, 2011). The rising rate of chronic pain has been accompanied by substantial increase in the use of prescription drugs, particularly opioids, and, unfortunately, a corresponding increase in their misuse. In 2010, 5.1 million Americans aged 12 years or older were current nonmedical users of prescription pain relievers, and 2.0

million were misusing them for the first time (Substance Abuse and Mental Health Services, 2011). Among emergency department visits in 2009 that resulted from the misuse or abuse of pharmaceuticals, about half involved pain relievers (Substance Abuse and Mental Health Services Administration, 2010). The most commonly reported pain relievers involved in emergency department visits contained oxycodone.

The balance between meeting the immense need for effective pain relief, the burden of prescription opioid misuse, and the associated potential serious adverse effects is a challenge to opioid formulators. Although the vast majority of pain patients do not misuse medications (Committee on Advancing Pain Research Care and Education Board on Health Sciences Policy, 2011), some patients and/or caregivers may inadvertently administer them by non-prescribed means (e.g., crushing instead of swallowing intact tablets). Conversely, recreational and experienced abusers may seek to alter controlled-release formulations for faster release of the active ingredient for oral use and, in many cases, for administration by alternate routes such as intranasal, injection, rectal administration, and smoking. These attempts at “tampering” with opioid

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formulations encompass many different methodologies ranging from physical manipulations such as chewing or grinding, to various extraction methods, and attempts at smoking. Thousands of postings on Internet websites are devoted to ongoing discussions regarding the best way to manipulate opioid formulations for the purpose of “getting high.” These sites have become a prime source of information for misusers interested in tampering with formulations (Cone, 2006).

Over the last decade, pharmaceutical manufacturers have developed a variety of proprietary formulations designed to impede or deter tampering attempts. These abuse deterrent formulations can be classified into groups that are broadly based on the use of physical barriers (tamper deterrent), inclusion of antagonists, inclusion of aversive agents, and use of prodrugs (Katz, 2008). Regardless of the specific approach, each formulation strategy can be viewed as the introduction of some impediment intended to mitigate either inadvertent or deliberate attempts at tampering.

Recently, the Food and Drug Administration published a draft guidance for industry for the assessment of abuse potential of drugs (Food and Drug Administration, 2010). This draft guidance included language on the laboratory assessment of abuse potential stating, “Information should be obtained on how much drug substance might be released and any changes that could take place in the rate of release of the drug from the drug product if it is misused either intentionally or unintentionally.” Further, the guidance called for assessments of various physical and chemical manipulations of the product matrix and the active pharmaceutical ingredient; however, there was no detailed guidance regarding how these assessments should be designed and conducted.

In 2007, Purdue Pharma L.P. submitted a New Drug Application for a reformulation of OxyContin (oxycodone HCl controlled release tablets, OP) to replace the then existing version of oxycodone controlled release (OC) medication. The product was subsequently approved in April 2010 and distribution began in August 2010. The reformulated OP version was designed to be bioequivalent to the original formulation and to be more difficult to manipulate for the purpose of misuse and abuse. The original version of OC was readily crushable, which would easily defeat the controlled-release mechanism and enable misuse and abuse through a variety of routes of administration. Misusers chewed or crushed the original formulation for oral use, crushed it for “snorting” (intranasal use) and dissolved the drug for injection. The OP reformulation incorporated new technology that imparted crush resistance, gelling properties when dissolved in small volumes of water, and retention of a degree of controlled-release properties after most physical and/or chemical manipulations. During the development of OP, Purdue Pharma L.P. faced a dilemma regarding how to objectively demonstrate that the reformulation exhibited greater tamper deterrent properties than the original OC product.

This report describes Purdue Pharma L.P.’s work in the development of a model for *in vitro* laboratory assessment of reformulated oxycodone. The goal of this report is to describe key elements of the model that were considered essential to the production of objective scientific data in laboratory settings that relate to “real-world” tampering attempts. The authors believe that many of the elements from this model are generally applicable to *in vitro* laboratory assessments of tamper deterrent properties of any product containing an active ingredient suspected to pose a risk for misuse and formulated with physical or chemical barriers intended to reduce that risk.

2. Methods

2.1. Model development

Given that it was not feasible to exhaustively study all potential tampering methods, a systematic approach was developed to evaluate a range of potential

methods that might plausibly be attempted by drug abusers. The basic concept for this model was that testing should be conducted in a laboratory setting in which various “tampering” attempts are studied in a stepwise fashion. The outcome of a particular tampering manipulation (which may involve a number of steps) would then guide the design of additional studies (iterations) of the same or similar manipulations. This approach is similar to that used in cyclic software development processes (Larman and Basili, 2003). Laboratory experiments were targeted toward outcomes that could produce tampered product suitable for administration by alternate routes. The resulting body of experimental data provided a systematic basis for assessing the overall “deterrent” properties of the formulation relative to the properties of the standard or control formulation. The goal of this approach was to define the strengths and failure limits of the product after physical and chemical manipulations.

2.1.1. Information gathering stage. To ensure that the testing program would be relevant and predictive of real world efforts practiced by substance abusers, it was necessary to gather information from several sources. This “information gathering stage” involved (a) reviewing information on the physicochemical properties of oxycodone, oxycodone hydrochloride, and formulation excipients, (b) reviewing scientific literature regarding common routes of abuse of oxycodone and other opioids, (c) surveying Internet sources on tampering methods employed on oxycodone and other opioids, (d) reviewing input from an external expert panel experienced in the chemistry of drugs of abuse and tampering methods, and (e) gathering information from ‘hands on’ manipulation scenarios and ‘how would you’ survey responses from actual drug abusers.

2.1.2. Manipulations. The design of laboratory protocols intended to simulate “real-world” tampering practices focused on methods that might be theoretically effective in converting OP into more abusable forms. Of particular focus were methods that might provide oxycodone in forms that would enable drug abusers to administer it by various routes of administration including intravenous injection, intranasal insufflation, rectal, and inhalation *via* smoking. Reformulated OP tablets were by design hardened so as to resist crushing with conventional tools. Furthermore, when hydrated in small volumes of aqueous media (as in preparation for injection), a highly viscous gel is formed. In contrast, the original (OC) formulation was easy to crush into a readily abusable powder that could be dissolved into a non-viscous solution for injection.

Initial experiments were conducted to determine how tablets could be reduced to particles potentially suitable for non-oral administration. Common household devices were tested including pill crushers, mortars and pestles, grinders, and graters. Materials resulting from physical manipulation of the tablets were separated into uniform “bands” of particle sizes. Standardized methods were developed to reproduce these discrete bands for use in subsequent experiments. The intact reformulated OP tablet and crushed original OC were included as controls. Studies included, but were not limited to, determining the rate of extraction of oxycodone from physically manipulated OP, determining the feasibility of preparation for injection, and determining the feasibility of abuse *via* smoking. Additional experiments explored manipulations such as oven-heating and microwaving.

2.1.3. Test and decision points. Interpretative criteria for success were generally based on whether a sufficient amount of drug was successfully released that might produce a desired effect. Study endpoints were set to help define decision points (>90% release in a controlled standardized testing environment). In the case of oxycodone, in which a known easily abused formulation was being replaced with a formulation designed to be tamper resistant, deterrence was considered achieved if the amount of drug released was considerably less than the original OC product and the manipulation was so difficult and complex that it appeared reasonable to assume that it would not be widely practiced (Cone, 2006). For this determination, a “deterrent” property was ascribed as the required amounts of experience, time, work, and resources increased substantially over that necessary for manipulation of conventional formulations that were not designed to be tamper deterrent. Additionally, if a minimum amount of drug considered likely to produce a psychoactive response in a non-tolerant individual (e.g., 5–20 mg of oxycodone by the intravenous route; Stoops et al., 2010) was not released then a 2nd iteration of the study would be considered.

2.1.4. Iteration. If the initial manipulation produced near failure of the formulation (i.e., >90% of oxycodone was released), no further iterations were considered necessary. If OP exhibited “deterrence” when subjected to an initial manipulation, a variety of changes in experimental design were considered that might enhance drug release (e.g., different pre-treatments, new solvents, pH adjustments, changes in isolation procedures). Iterations were then performed on those manipulations which appeared to have the potential to overcome formulation deterrence.

2.2. Scientific design validity

Protocols for laboratory tamper assessments of OP were designed by Purdue Pharma L.P. with input and concurrence from the Food and Drug Administration to provide reliable, accurate data. [This approach and the findings were presented to the Food and Drug Administration and an FDA Advisory Committee

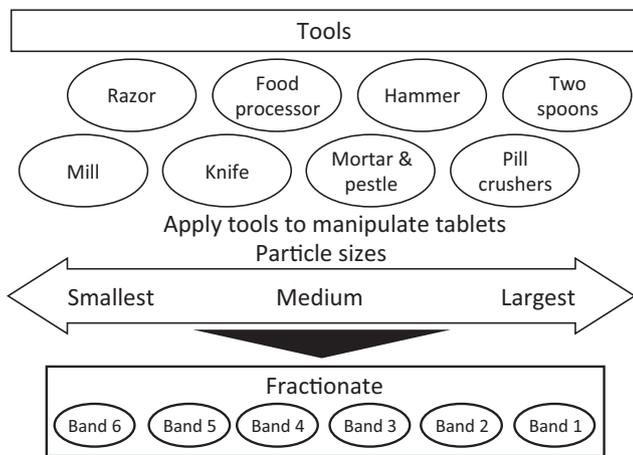


Fig. 1. Approaches to tablet manipulation by common methods (laboratory standardization of “real world” tablet manipulation).

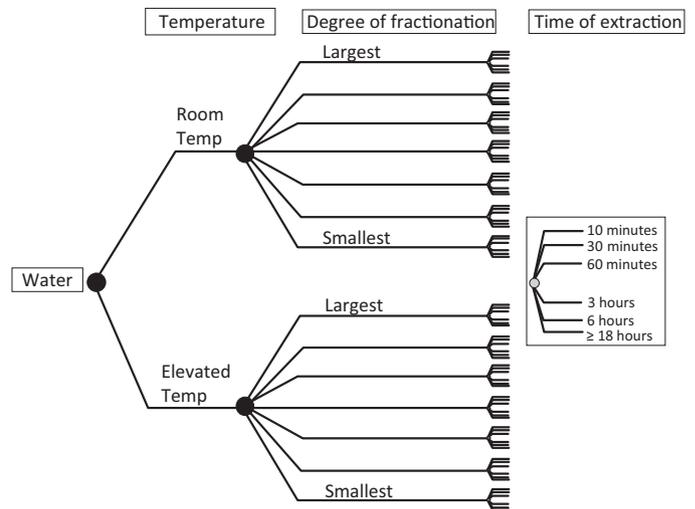


Fig. 2. A general extraction scheme for studies in water.

(September 24, 2009). Those comments are in the public domain: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM187629.pdf>.] The experimental design of each protocol included the following elements: testing of all dose strengths; use of sufficient replicates for evaluation of method variability; inclusion of adequate controls for comparison of results; investigation over a range of chemical and physical conditions; experimentation over adequate time periods to determine failure limits; verification of analytical methods; and use of independent laboratories to whom the methodologies had been transferred.

3. Results

3.1. Implementing model testing

OP was tested under a broad range of manipulations including particle size reduction, extractions in household and laboratory solvents, and effects of extreme temperatures on drug release. Frequently, sequences of physical and/or chemical steps were incorporated into “multi-step manipulations” (e.g., tablet crushing followed by a simple or complex extraction sequence). Experiments were run in sufficient replicates to statistically assess imprecision, resulting in robust datasets. For example, using 5 replicates of each dosage strength for each condition tested during small volume extraction resulted in collection of over 10,000 data points for this study alone. Results of manipulated product were compared to original OC and to intact reformulated OP tablets. The degree to which the labeled dose of OP was released after manipulation sometimes led to additional iterations using new conditions.

3.2. Particle size reduction methods

A variety of household tools were used in attempts to crush or grind OP tablets. Because of their hardened nature, simpler methods which were successful in crushing original OC tablets (e.g., spoon) were unsuccessful with the reformulated product. As shown in Fig. 1, more elaborate household appliances were needed. Different appliances produced characteristic mixtures of particles with different distributions of particle size. Fig. 1 further illustrates the spread of particle size ‘bands’ that were produced by various types of appliances. At the largest end of the particle size spectrum, an intact deformed tablet was produced. To achieve the smallest fraction, mechanical manipulation using electrical appliances was required to create a particle size output that could be portioned into a smallest fraction (<600 μm) for evaluation. Ground particles were separated by sieve analysis into a series of bands each containing a set distribution of particle sizes. This process resulted in the standardized creation of six relatively uniform and distinct particle

size bands. Overall, generating test articles for OP required more sophisticated mechanical means. This was in contrast to the simplicity of reducing the OC formulation to a fine powder with a spoon or a credit card. These efforts indicated that the reformulated product required considerably more time, effort and resources to reduce the tablet to small particles compared to the original formulation.

3.3. Extraction studies

Water is the most commonly utilized solvent in various tampering methods and its potential use to extract oxycodone from OP was studied extensively under a variety of conditions. The effects of solution temperature (room temperature and near boiling temperature), particle size, and time of extraction (10 min to >18 h) were studied. Fig. 2 illustrates a general extraction scheme that was utilized for water extraction studies. The time course of the extraction was monitored for at least 18 h or until >90% of the oxycodone dose had been extracted.

Additional extraction studies (illustrated in Fig. 3) conducted using an abbreviated design were performed in (a) aqueous media at different pH conditions at room temperature and near boiling temperature, (b) extraction with household solvents at room and elevated temperatures, and (c) complex extraction protocols that

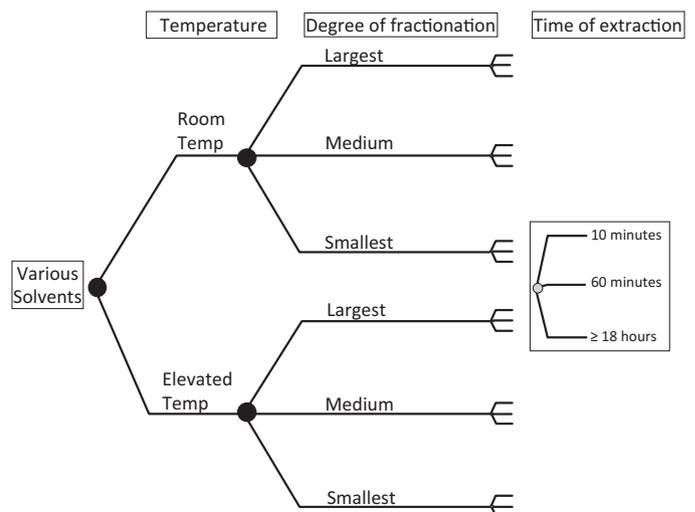


Fig. 3. An abbreviated extraction scheme for solvents other than water.

involved both aqueous solution and extraction with immiscible organic solvents.

The results of these studies indicated that it was considerably more difficult to extract oxycodone from OP than from the original OC formulation. Further, the OP formulation, even when reduced to particles, retained some controlled-release properties.

3.4. Syringeability and injectability studies

Because OP produced a viscous hydro-gel in small volumes of water, laboratory studies were designed to evaluate the feasibility of preparation of an injectable dose of oxycodone. Initial attempts to prepare a solution for injection with the smallest sized band in 2 mL of water were unsuccessful. Two protocols were designed that utilized larger volumes of solution (5 mL and 10 mL of water). "Syringeability" was assessed by mixing the smallest sized band with water at room temperature or after boiling. Following this step, the solution was attempted to be aspirated into syringes fitted with different gauge needles. Aspiration was conducted continuously for 1 min. Results were assessed by assaying the amount of oxycodone drawn into the syringe as well as the volume of aspirate. "Injectability" was assessed by back loading the solution into the syringe barrel, replacing the plunger, and attempting to eject the solution through different gauge needles. Results were assessed by measuring the amount of oxycodone ejected from the syringe. These studies demonstrated that the hydro-gelling characteristics of the reformulated OP product caused difficulty in attempts at preparation of the product for injection.

3.5. Vaporization experiments

The process of "smoking" a drug involves application of a heat source that is sufficient to vaporize a portion of drug in a "localized" manner such that the resulting vapor can be inhaled. Typically, drug product is placed on a metal surface and heat is applied while an individual attempts to inhale the vapor. In the laboratory, this process can be simulated by heating drug in a test tube and capturing the volatilized drug in a confined air space above the product. Preliminary studies identified the optimum heating conditions of physically manipulated OP. Control materials included original OC (crushed), oxycodone HCl, and oxycodone base. Only a small portion of oxycodone from OP (<20%) was vaporized following heating. The remainder of the oxycodone HCl dose was decomposed.

These studies demonstrated that simulated attempts at "smoking" the reformulated OP product produced only minimal volatilization of oxycodone HCl.

3.6. Dissolution studies

The possibility that co-ingestion of ethanol may modify the *in vitro* release characteristics of the formulation, where dose dumping may be an issue for patient safety, was investigated (Walden et al., 2007). Dissolution tests were conducted in simulated gastric fluid (SGF) and with a mixture of ethanol and SGF (ethanol/SGF). The tests were performed with intact tablets and with the six particle size bands. Generally, OP dissolution rates in ethanol/SGF media were slower than that seen in SGF alone. This indicated that "dose dumping," or an increase in the release rate over that resulting from dissolution in the media (SGF) alone, was unlikely to occur with ethanol use.

3.7. Summary of tampering results

The approach of this paper is to discuss scientific parameters of tamper testing procedures but not to publish specific methods

or results. OP exhibited a substantial level of deterrence to many tampering methods but extraction was not impossible, nor would the formulation be expected to impair abuse by oral ingestion of intact tablets. Physical manipulations of OP that involved cutting or grinding tablets were considerably more difficult and required more time, effort, and specialized equipment than with OC. Extractions with aqueous based solvents were complicated by the hydro-gelling properties of the OP formulation, particularly when smaller volumes, such as those used in preparation for injection, were employed. The high viscosity of the resulting solutions impaired syringeability and injectability. More complex extraction schemes occasionally produced greater release of drug, but resulted in preparations that were unsuitable for immediate use. Laboratory experiments designed to simulate "smoking" conditions produced low recoveries of volatilized drug indicating that the OP formulation would be inefficient for abuse *via* smoking. Dissolution experiments indicated that co-administration of alcoholic beverages with intact or physically manipulated OP formulation would not likely result in "dose dumping" due to the presence of alcohol.

4. Discussion

4.1. Laboratory testing and "real-world" tampering

From the developers' and regulators' point of view, opioid product development, until recently, has been primarily focused on the pharmacokinetic and pharmacodynamic properties exhibited by the product when used according to labeled instructions. Some discussion has also taken place regarding the impact of formulation on abuse potential and safety of opioids. For example, a 2006 Expert Panel report (Grudzinskas et al., 2006) indicated consensus that formulations of abused substances could be developed that would decrease its abuse potential while retaining full clinical efficacy. Numerous manufacturers have explored development of new formulations specifically designed to provide tamper deterrent properties (Hamed and Moe, 2010). Initially, most development efforts focused on controlled-release opioid formulations because of the high dose load. Modification of a controlled-release formulation by crushing or other forms of "tampering" presents the risk of partial or complete conversion of the controlled-release properties to a product that resembles an immediate release product. Depending upon the circumstances, tampering with an opioid medication can bring about tragic results such as overdose and death.

The development of tamper deterrent products has led to the call for standardized laboratory methods for their assessment (Grudzinskas et al., 2006; Katz et al., 2007). Mansbach and Moore (2006) stated that "standardization of methods to understand the consequences of product tampering could assist in gaining a better assessment of risk for controlled release formulations". Given the wide array of potential tamper deterrent products currently in development, it is unlikely that a "standardized battery" of laboratory tests would apply to all products.

The model described in this work represents a divergence from the assumption that a "standardized battery" of tests can be developed for *in vitro* assessment of tamper deterrent products. The model utilizes a conceptual approach to design, implementation, and interpretation of laboratory experiments that challenge formulations in ways related to "real-world" tampering scenarios. In fact, the model has similarity to tampering practices as often described in Internet postings. Individuals interested in "tampering" with a drug formulation will frequently post Internet queries regarding what methods are successful (information stage). The individual may then attempt a procedure (manipulation stage) and self-administer the tampered product (test stage). Depending upon the perceived effect, they may report success (drug release

stage) or failure (deterrence stage) due to limited effect or adverse consequences. Others may comment on posted drug tampering reports, discussing probable causes of failure or success and even suggesting new approaches. Motivated individuals often repeat this cycle (iteration stage) multiple times in their quest to discover successful tampering methods.

4.2. Interpretation of laboratory tests

Table 1 summarizes some of the physical and chemical methods used in the laboratory for tamper assessment of a controlled-release product containing oxycodone and how these methods relate to common routes of administration practiced by misusers (Young et al., 2010). Tampering efforts are conducted on controlled-release opioid formulations for different anticipated goals. Such efforts frequently focus upon disruption of the formulation matrix in ways that provide greater access to the active ingredient. The simple act of crushing a tablet leads to creation of smaller particles and greater surface area which may accelerate drug release and absorption and a faster onset of desired effects. It is generally believed that opioid euphoric effects are positively related to the speed in which the drug enters the brain and its consequent reinforcing and mood altering effects (Schuster, 2006). Recently, Comer et al. (2009) demonstrated that the subjective and reinforcing effects of oxycodone increase with shorter infusion durations (e.g., visual analog ratings of drug liking were significantly greater following a 2 min infusion period compared to longer periods; 15, 30, 60 and 90 min). Thus, many tampering attempts appear to be directed toward alteration of the controlled-release properties of opioid formulations to those more resembling an immediate release product.

4.3. Conclusions drawn from laboratory assessments of OP

The body of data collected for OP tablets demonstrated that the formulation is more difficult than OC to manipulate and requires time, effort, experience, and tools. Overall, this suggested that OP is an incremental improvement when compared to the original product (1) for individuals who attempt to alter the formulation for purposes of misuse and (2) for patients who sometimes inadvertently misuse for ease of use (e.g., crushing and placing in apple sauce which is acceptable for many immediate release formulations).

Recent findings on abuse rates and routes of administration in the 20 months following OP introduction into the marketplace support these predictions from the laboratory assessments. Initial results suggest that abuse of the OP formulation reported in substance abuse treatment patients has declined as compared to the original OC formulation and, among patients who abused the OP formulation, the proportion also declined for those who abused the reformulated product by non-oral routes (injection, nasal, smoking; Chilcoat et al., 2012).

4.4. Limitations in laboratory procedures for assessing tamper deterrence

As drug abusers can be creative, persistent, and highly motivated, it is unlikely that any feasible program of premarket testing can exhaustively assess every conceivable tampering method that might be explored; however, comprehensive information gathering as described in this report offers a systematic approach to designing laboratory testing for premarket product evaluation. Internet procedures are rarely written in sufficient detail to be replicated in a laboratory setting. Descriptions of tampering procedures (“recipes”) often leave out crucial details such as time, temperature, equipment, and purity of solvents. Consequently,

whether any laboratory experiment replicates a “real-world” scenario is questionable. Despite these limitations, well-designed laboratory experiments yield useful, relevant information regarding the strengths and weaknesses of new formulations. *In vitro* laboratory studies should be meaningful and directionally predictive of follow-up *in vivo* studies including pharmacokinetic testing (bioavailability of intact or manipulated tablets by oral and intranasal routes) and abuse potential studies (pharmacodynamic profiling incorporating various subjective measures, i.e., liking studies). Cumulatively, the outcomes of these pre-marketing evaluations should provide an understanding of the possible overall abuse potential of the product studied in post-marketing epidemiology studies. These studies are necessary to fully understand the ‘real world’ impact of the formulation. That being said, the predictive value of laboratory test results in determining whether a product will be abused and by what routes is uncertain. What can be safely assumed is that formulations with potentially abusable ingredients will be subjected to many chemical and physical challenges. It is impossible to anticipate and evaluate in an *in vitro* testing program all possible methods of tampering. It is possible that certain formulation weaknesses might remain undiscovered in laboratory assessments but be uncovered through the many trial and error attempts by individuals engaged in tampering practices. Comprehensive evaluation according to an information-guided, iterative model is intended to minimize this risk but cannot completely rule out the risk. Finally, it should be understood that individuals who are highly motivated can, with sufficient expertise, time and resources, develop means of isolating and purifying almost any active ingredient from a formulation matrix. At the same time, formulations with built-in tampering barriers may restrict or deter many individuals who otherwise might have altered a formulation for abuse purposes. From a public health and drug control perspective, then, the metric for success of a formulation should not be, “is tampering possible?”, but instead, “will the new formulation provide an incremental barrier of such magnitude that real world abuse and harm will decline?”

One indirect measure that may be predictive of this outcome is the reduced street value of the OP formulation. Recent findings (Severtson et al., 2012) comparing the street price of the original OC formulation to reformulated OP and immediate release (IR) oxycodone products suggest that the OP formulation has less street value per milligram of active ingredient than other drugs within the oxycodone drug class. The street price of OP was 22% lower than the street price of the original OC formulation in the post introduction OP time period. Following the introduction of OP, the street price for IR oxycodone products is higher than those in the pre-OP period. The findings suggest that there is less demand for OP through illicit channels than the original OC formulation. There may also be increase in demand for other oxycodone products. However, price is determined by supply and demand of a product and the relative role of each factor in the price changes caused by the introduction of OP is unknown.

Another indication of tamper deterrence is to assess changes in poison center exposure cases reported to the American Association of Poison Control Centers’ National Poison Data System. Intentional abuse exposures reported to Poison Centers are a proxy measure for adverse events associated with abuse. A study that compared poison center data (Coplan et al., 2012) for oxycodone indicated there was a decline in the number of intentional abuse exposures for oxycodone from before to after the introduction of reformulated OP. During the same time period there was an increase for the comparator opioids of other single-entity oxycodone products and heroin from before to after introduction of OP. In addition, there was a decline in unintentional therapeutic errors, a proxy measure of safety in patients, for OP but not for other single-entity oxycodone

Table 1
Suggested laboratory procedures for assessment of a controlled-release opioid formulation.

Route	Physical method	Chemical method	Laboratory assessment
Oral	Intact	N/A	Dissolution in SGF ^a and SGF/ethanol
Oral (chew)	Crush	N/A	Manual tools and electric devices followed by dissolution
Oral (drink)	Crush	Solutions	Aqueous and ethanol extractions
Nasal	Crush	Extractions	Extraction in small volumes of aqueous media
Injection	Crush	Extractions	Simple and complex extractions with water and organic solvents; syringeability and injectability studies
Rectal	Crush	Extractions	Manual tools and electric devices followed by aqueous extractions
Smoking	Cut; crush; vaporize	Salt; conversion to free base	Complex extractions; precipitation studies
Buccal, sublingual	Crush	Solutions	Solubility and dissolution in small volumes of aqueous and ethanolic media

^a Simulated gastric fluid.

products. There was a decline in unintentional general exposures for OP, which includes accidental ingestion by children, but not for other comparator opioids. Heroin abuse and other single-entity oxycodone abuse increased after introduction of the new formulation. Although these had been increasing prior to OP introduction, the rate of increase of heroin abuse accelerated after OP introduction. Continued post marketing surveillance of abuse and diversion is ongoing.

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Contributors

All authors contributed to and have approved the final manuscript.

Dr. Edward Cone is an independent consultant from Pinney Associates. As a Pinney Associates consultant, he assisted in the development, validation, and testing oversight for abuse resistance testing of oxycodone formulations. Pinney Associates was compensated by Purdue Pharma L.P. for this project.

Conflict of interest

Jennifer Giordano and Brianne Weingarten are both employees of Purdue Pharma L.P. and have no conflicts of interest.

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