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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.

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