

BACKGROUND PAPER FOR FDA GUIDANCE DOCUMENT

I. INTRODUCTION

This document provides background and structure for the FDA to support development of a Guidance Document to industry on the development of abuse-deterrent formulations (ADFs) of prescription opioid products. It accompanies a Citizen Petition that requests the Agency to publish such a Guidance Document and to promote related incentives for industry to develop the ADFs. Content for both documents grew out of a meeting organized by the Tufts Health Care Institute in November 2006. Meeting participants are listed in Appendix 1. Details of the Meeting, including individual presentations can be accessed at http://www.thci.org/opioid/opioid_nov06.asp.

Opioid analgesics are an essential cornerstone in the management of pain, and increasing access to opioids is deemed an important step on the road to reduced pain and suffering. Availability of these drugs has improved markedly over the past several decades¹; however, such access is also associated with a dramatic rise in prescription opioid abuse (POA)², and has had consequences that include death³, non-fatal poisoning², addiction², entries into substance abuse treatment programs⁴, teenage suicide⁵, accidental pediatric ingestion⁶, direct health care expenses⁷, and societal costs⁸. The term “abuse” is used in diagnostic coding systems to refer to a specific substance use disorder⁹; however, in this document, we use “POA” as an umbrella term that refers to a group of behaviors displayed by individuals who may or may not be patients prescribed the medication, and who use the drug in a non-medically appropriate manner for the

¹ World Health Organization: Achieving balance in national opioids control policy: guidelines for assessment. Document WHO/EDM/QSM/2000.4.

² Overview of Findings from the 2004 National Survey on Drug Use and Health; revised September 8, 2005.

³ Paulozzi LJ, Budnitz, DS, Yongli YX. Increasing deaths from opioid analgesics in the United States. *Pharmacoepidemiol Drug Saf* 2006; 15(9):618-27.

⁴ Treatment Episode Data Set (TEDS) Highlights – 2004. National Admissions to Substance Abuse Services. Dept. of Health and Human Services. Available at <http://www.dasis.samhsa.gov/teds04/tedshigh2k4.pdf>. Accessed December 7, 2008.

⁵ Disposition of emergency department visits for drug-related suicide attempts by adolescents: 2004. V The New DAWN Report 2008; Issue 6.

⁶ Watson WA, Litovitz TL, Rodgers GC, Kelein-Schwartz W, Reid N, Youniss J, Flanagan A, Wruk KM. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System *Am J Emerg Med* 2005; 23(5):589-666.

⁷ White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, Katz N. Direct costs of opioid abuse in an insured population in the United States. *J Manag Care Pharm* 2005; 11(6):469-79.

⁸ Birnbaum HG, White AG, Reynolds JL, Greenberg PE, Zhang M, Vallow S, Schein JR, Katz NP. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. *Clin J Pain* 2006; 22(8):667-76.

⁹ DSM-IV Substance Abuse Criteria: http://www.dawnfarm.org/pdf/DSM_Abuse_and_dependence_criteria.pdf; Accessed December 7, 2008.

purpose of experiencing the psychoactive properties of the product¹⁰. Behaviors encompassed under POA include chewing and swallowing an extended-release formulation to accelerate onset, taking several doses of an intact immediate-release product to experience euphoria, crushing a formulation and snorting it, dissolving an extended-release formulation and injecting it, or co-ingesting a prescription opioid with alcohol or other drugs to increase euphoria.

This background paper reviews currently recognized types of POA and offers a conceptual framework that may be used to establish deterrence potential for each formulation in relation to the subtypes of abuse. Note that we do not draw a distinction between *abuse deterrence* and *abuse resistance* – the terms are used interchangeably here. We also present types of statements that can be considered for inclusion in a product label, and outline the evidence required to support such statements. The current phenomenology of POA will undoubtedly continue to be clarified, and POA itself will evolve over time, as will types of formulation approaches that are developed to address this problem and the design and interpretation of studies conducted to elucidate the properties of putative ADFs. We thus do not attempt to comprehensively and permanently cover all possible development scenarios; rather we offer a general plan for consideration of these issues, one that will have to be reduced to specific guidance in the context of each specific product.

II. TYPES OF PRESCRIPTION OPIOID ABUSE

II a. Ingestion of intact formulations

Most individuals in the US who acknowledge non-medical use of prescription opioids ingest the formulation intact, and several sources indicate that, even among individuals in treatment for substance abuse, the oral route dominates^{4,11}. In the Treatment Episode Data Set (TEDS) almost three-quarters (72 percent) of primary non-heroin opiate admissions report oral ingestion as the route of administration, 13 percent report inhalation, and 12 percent report injection^{4,11}. Little information is available on routes of administration among less advanced abusers and among patients; however existing data suggest that oral ingestion is even more common among such individuals^{11, 12}. And although ingestion of intact formulations is likely to be less dangerous than more advanced methods such as snorting and injection, abuse by the oral route is nonetheless problematic, since it is widely endorsed as the primary route of administration by the majority of both early and advanced users. Thus, the design of formulations that deter ingestion of excessive quantities of opioids, or that are safer after such intake, is a worthwhile undertaking.

¹⁰ Katz NP, Adams EH, Chilcoat H, Colucci RD, Comer SD, Goliber P, Grudzinskas C, Jasinski D, Lande SD, Passik SD, Schnoll SH, Sellers E, Travers D, Weiss R Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain* 2007; 23(8): 648-60.

¹¹Butler SF, Budman SH, Licari A, Cassidy TA, Liroy K, Dickinson J, Brownstein JS, Benneyan JC, Green TC, Katz N. National addictions vigilance intervention and prevention program (NAVIPPRO™: a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf* 2008; 17(12):1142-1154.

¹² Katz N, Fernandez K, Chang A, Benoit C, Butler SF. Internet-based survey of nonmedical prescription opioid use in the United States. *Clin J Pain* 2008; 24(6):528-35.

II b. Chewing.

Few, if any, published investigations exist on the frequency of chewing as a method of ingestion of prescription opioids, or on the pharmacology of opioids ingested by this route. A recent survey of nearly 1000 prescription opioid abusers found that approximately 20% of hydrocodone-acetaminophen users and 30% of extended-release oxycodone users chew their formulations, presumably to accelerate onset and peak effect¹². Since accelerated onset or increased maximal exposure may be expected to increase the likelihood of negative consequences of prescription opioid abuse, including overdose and addiction, the design of products whose pharmacokinetics are difficult or impossible to alter through crushing or chewing comprises another target of ADF development.

II c. Crushing and snorting

Crushing and snorting is a method of ingestion reported by a subset of abusers who begin with oral intake^{Error! Bookmark not defined.}. According to TEDS, approximately 1/3 of individuals in treatment for prescription opioid addiction indicate snorting (referred to as "inhalation" in the report) as their route of ingestion⁴. In addition to the negative consequences of faster onset and greater maximal exposure that result from snorting, inhalation-related complications also include nasal and palatal perforations¹³. Thus, designing products that are difficult or impossible to crush into a form that can be snorted is a goal of formulation development.

II d. Injecting oral or transdermal formulations

Use of the intravenous route of administration may parallel increasing levels of addiction¹¹, and may be accompanied by serious co-morbidities (HIV, hepatitis, pancreatitis) as well as societal and law enforcement consequences⁷. Oral formulations are prepared for injection by abusers using a variety of means that include mechanical manipulation (crushing or otherwise disrupting the dosage unit), followed by single- or multiple-step chemical manipulations for dissolving the dosage unit in a common solvent such as water or alcohol¹⁴. In the NAVIPPRO database of individuals that are primarily in addiction treatment, approximately 29% of extended-release oxycodone abusers and 65% of extended-release morphine users report injecting their products¹⁵. Intravenous injection of prescription opioids is a public health problem unto itself, and designing products that are difficult or impossible to prepare for intravenous injection is yet another aim of ADF development.

II e. Co-ingestion with alcohol or other drugs of abuse

A number of sources indicate that co-ingestion of alcohol with prescription opioids is an aspect of POA that also presents public health risks. A significant number of individuals abuse both prescription opioids and alcohol: about 20% of emergency department visits related to

¹³ Greene D. Total necrosis of the intranasal structures and soft palate as a result of nasal inhalation of crushed OxyContin. *Ear Nose Throat Journal* 2005; 84(8):512-16.

¹⁴ Katz NP, Buse DC, Budman SH, Wing Venuti S, Fernandez KC, Benoit C, Bianchi R, Cooper D, Jasinski DR, Smith DE, Butler SF. Development and preliminary experience with an ease of extractability rating system for prescription opioids. *Drug Dev Ind Pharm.* 2006; 32(6):727-46.

¹⁵ Personal Communication, Stephen Butler, Inflexxion, Inc.. Presented by Katz NP at FDA CDER Advisory Committee Meeting, November 14, 2008; Transcript pages 44-60.

prescription opioid ingestion are associated with concomitant alcohol ingestion¹⁶. Co-ingestion of alcohol along with extended-release prescription opioids can compromise the formulations and may lead to accelerated release of the opioid, with potentially serious consequences. One such product was removed from the market in 2005^{17,18}. Both alcohol and prescription opioids suppress respiratory and cardiovascular centers, and may increase the probability of fatality by acting synergistically. The design of products that are safer when co-ingested with alcohol is thus an appropriate direction for ADF development.

In practice, preferred routes of administration appear to be product-specific: for example, oxycodone-ER is primarily injected or snorted, whereas immediate-release hydrocodone combination products are predominantly ingested orally, with only 1% of abusers using the intravenous route¹¹. Gaining insight into how a specific opioid is abused is an essential prerequisite for developing abuse deterrence: thus, for the example discussed in **II d** above, designing injection-resistant formulations of oxycodone-ER would be warranted, but developing a similar formulation of hydrocodone-acetaminophen would have little public health impact, since this product is rarely injected. Moreover, depending on the goal of the product design, more than one approach to deterring abuse may be incorporated into a single formulation.

III. APPROACHES TO ABUSE DETERRENCE

Many conceptual approaches exist for achieving abuse-deterrence in an opioid formulation. Several categories of such approaches are listed in Table I and are described in further detail below.

Table 1: Potential formulation-specific clinical benefits*.

	1	2	3	4
Type of abuse affected	Decreased extractability	Addition of aversive compounds	Agonist-Antagonist Combination	Prodrug
Intact Oral	-	+	-	+
Crushed/chewed oral	+	+	+	-
Crushed/snorted	+	+	+	-
Dissolved/injected	+	+	+	+
Co-ingested with Alcohol	+	+	+	-

*The table is supplied to illustrate a conceptual framework, not to suggest that such advantages have been demonstrated.

¹⁶ The New DAWN Report, Emergency Department Visits Involving Nonmedical Use of Selected Pharmaceuticals, Issue 23, 2006.

¹⁷ FDA News: FDA asks Purdue Pharma to withdraw Palladone for safety reasons. PO5-42, July 13, 2005. <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01205.html>, accessed December 7, 2008.

¹⁸ Paulozzi LJ. United States Senate Subcommittee on Crime & Drugs Committee on the Judiciary and the Caucus on International Narcotics Control. Trends in Unintentional Drug Overdose Deaths. CDC Congressional Testimony, March 12, 2008. <http://www.cdc.gov/Washington/testimony/2008/t20080312a.htm>, Accessed December 8, 2008.

III a. Formulations that Resist Physical/Chemical Manipulation

The goal of developing such products is to thwart the alteration of release dynamics of the active pharmaceutical ingredient (API), or to prevent administration of the API via unintended routes. For instance, an opioid designed to be swallowed may also be crushed and injected, crushed and snorted, or chewed. Formulations that are targeted at averting these types of abuse are thus designed to reduce the vulnerability of the product to commonly performed mechanical, chemical, thermal, or other manipulations (Table 1, column 2). Various approaches to hindering these behaviors have been considered, including the use of gummy or hard formulations that resist crushing, and the addition of excipients that resist rapid extraction of the API in commonly available solvents or that render a formulation too viscous to be drawn up into a syringe after attempted dissolution. The value of these formulations is predicated on the assumption that creating roadblocks to tampering will render a formulation less abused in the community, though validation of this assumption will require direct evidence of such an effect. At the same time, however, these formulations must be designed such that the API, when taken via the intended route, is eventually released to provide the analgesic effect.

III b. Aversive Formulations

These products contain an aversive compound, and are developed to be safe and effective as analgesics when administered as intended, but to release the aversive compound when excessive quantities are ingested, or when the dosage unit is manipulated for the purpose of abuse. Several approaches are being considered, including incorporation of capsaicin (which is released upon crushing to trigger a severe burning sensation if sorted or injected), combination with a bitter ingredient to deter abuse via oral route, addition of an emetic or a malodorous substance (to cause nausea, and thus deter chewing), or inclusion of niacin (to cause an uncomfortable “niacin reaction” when ingested in excess, and to deter such experiences in the future) (Table 1, column 3). Challenges in designing these formulations include the additional burden of proof imposed on developers to demonstrate that the intended population suffers neither additional adverse effects nor any loss of efficacy in using these products: the degree to which such products actually deter abuse cannot be readily assumed.

III c. Agonist-Antagonist Combinations

These compounds are designed so that an opioid antagonist incorporated into the formulation is not bioavailable when the opioid is administered under intended conditions, but attempts to manipulate the product lead to activation of the antagonist (Table 1, column 4). The formulations may be achieved via various means, such as incorporation of a sequestered antagonist that is only released when the formulation is manipulated, or of an antagonist that is not orally bioavailable but is released when the product is administered via the intravenous or nasal routes. Agonist-antagonist compounds are designed to negate the euphoria associated with abuse of the drug, but in some cases they may also produce frank withdrawal. A potential advantage of these products is that the antagonist and agonist are designed such that they are difficult to separate without elaborate extraction procedures. However the sponsor has an additional burden of proof in determining that the antagonist produces no additional safety or efficacy limitations.

III d. Prodrugs

A prodrug is a precursor of a drug that must be metabolically converted into an active pharmacological agent¹⁹. If enzymes in the gastrointestinal tract or in the plasma that metabolize the prodrug are saturable, then exposure to the active moiety will, in principle, also saturate when a threshold dose has been reached. When ingested orally, such a formulation would confer overdose protection and ceiling effects of other toxicities; however, this characteristic would also limit titrating to higher doses for therapeutic purposes (Table 1, column 5). Prodrugs are of special interest in the prevention of overdosing: no other ADF designs confer overdose protection for drugs that lack intrinsic ceilings for toxicity.

IV. TYPES OF EVIDENCE REQUIRED FOR DEMONSTRATION OF ABUSE DETERRENCE

Robust scientific evidence from adequate and well-controlled studies is needed to document that a product has abuse-deterrent features. The spectrum of such evidence, generated to support different types of assertions about deterrence, can be classified according to five general categories: results from benchtop studies, preclinical studies, human abuse liability studies, clinical trials, and epidemiological studies. Figure 1 indicates a rubric for how these evidence categories fit together in a continuum. From left to right, the data sources are arrayed in order of increasing persuasiveness with respect to public health relevance (external validity); data from studies listed further to the left are more easily obtainable and are more internally valid. Results derived from evidence categories that are further to the right of the conceptual schema are more likely to support explicit claims, whereas those from categories towards the left would, at most, support descriptions of studies in the product label.

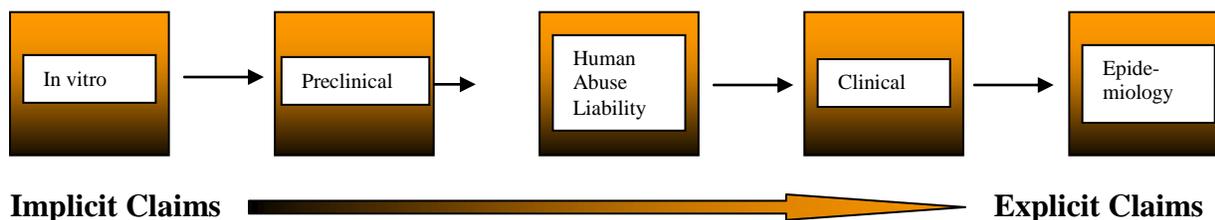


Figure 1. Totality of Evidence

Studies purporting to inform about abuse liability should strive to meet a number of criteria: i) they should be *comprehensive*, in that all relevant forms of abuse should be studied; for example, an *in vitro* extractability battery should incorporate all commonly available solvents, not just an arbitrary selection; ii) they should be *relevant for common types of abuse*: thus, for example, abuse liability evaluations of agonist-antagonist combinations should assess whether targeted reductions in euphoria occur subsequent to all relevant routes of administration; iii) they should be *tailored to specific product characteristics*: for example, standard extractability tests that show imperviousness to an array of solvents would not be complete for a product that is easily

¹⁹ Webster's medical online dictionary. <http://www.medterms.com/script/main/art.asp?articlekey=23992>; Accessed on January 7, 2009.

defeated with simple mechanical manipulations; iv) they should be done according to *standard scientific methodologies*, including, as appropriate, prespecification of methods, measures, and endpoints; randomization; blinding; and use of validated outcome measures; v) important results should be *confirmed independently*; and vi) the experimental program should be *conceptually connected to the public health benefits* that each product purports to provide: for example, demonstrating that an immediate-release opioid combination product cannot be easily dissolved and injected would have little potential public health value, since these products are rarely injected at present: however, documenting a ceiling effect for the toxicity of such a product could provide an extremely valuable public health advantage.

V. CLAIMS AND LABELING

Sponsors seek the translation of clinical benefits associated with novel ADFs into claims that can be listed in drug labels; opportunities for including new labeling claims, and for targeting these claims early during the drug development process, offer powerful incentives to industry for seeking, developing and commercializing ADFs. Scientific evidence to support a tangible relationship between the types of experiments that can be conducted to predict real-world abuse and the real-world abuse that actually occurs is limited; this lack hinders the determination of when it is appropriate to include descriptions of such experiments or their implications in a package insert. Furthermore, lack of clarity about the beneficiaries of putative product advantages (all patients, only high risk patients, only non-patients, etc.) has made decisions about labeling more complex.

As detailed in a recent publication²⁰, two types of fact-based labeling statements may result from abuse-deterrent methodologies: i) Implicit claims refer to data that *might* be linked to abuse; such claims could “hypothetically include product descriptions (‘formulated with an added ingredient in order to deter abuse’), summaries of extractability testing (‘does not dissolve in alcohol’), summaries of human liability studies (a trial showed less “liking” than an active comparator’), and summaries of potentially abuse-related adverse effects (“no euphoria or similar adverse effects seen in clinical studies”)^{10,20}. Implicit claims may be included in the *Drug Abuse and Dependence* section, the *Warnings, Precautions, Black Box* section, or in the *Description* section of the label. ii) Explicit claims are based on direct documentation of reduced abuse with the novel formulation in relation to a comparator drug. Prolonged, well-controlled, clinical or epidemiological studies are needed to establish such a relationship, and no consensus exists on methods that are appropriate for conducting definitive studies of this type²⁰. Below, we provide broad guidance for the types of evidence needed to support Implicit and Explicit claims; this guidance is outlined with the recognition that, in the early stages of development of such research methods, programs will need to be considered on a case by case basis, and standards in this field will likely evolve rapidly.

V a. Claims Based on Testing for Benchtop Tampering/Extractability

Extractability refers to making available usable quantities of API relevant to substance abuse from a formulation¹⁴. Extractability consists of at least four dimensions: ease of extractability,

²⁰ Katz NP, Adams EH, Chilcoat H et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain* 2007; 23:648-660.

purity of the extract, efficiency of the extraction process, and the potency of the resulting product. It is widely accepted that individuals with substance abuse disorders prefer products with fast onset (Tmax) and high degrees of exposure (Cmax)²¹, and that they will manipulate prescription drug formulations in order to “improve” product pharmacokinetics, often by altering the route of administration. Products that are more extractable have been shown to be more attractive to abusers, although this may vary by subpopulation²². Extractability is thus presumed to be related to abuse liability, and scheduling decisions have been made in part on extractability²³. The term “tampering” (or “tamperability”) is used primarily to focus on thwarting the delivery system: for example, to defeat a metering system into releasing more than the prescribed dose, or to bypass a controlled release mechanism. Unfortunately, however, use of this term creates the possibility of confusion with the phrase “tamper-resistant packaging”. Since there is no consensus on use of this terminology, the two terms are often used interchangeably.

Extraction procedures described in the literature^{14, 24} generally fall into the following categories: physical manipulation (e.g. chewing, crushing, cutting); single-step chemical manipulation (e.g. dissolving in water); multi-step chemical manipulations (e.g. dissolving in alcohol, evaporating, then dissolving in water); and complex laboratory extractions¹⁴. A core Standardized Extractability Battery has been proposed^{14, 24}, but no battery, however complete, can substitute for a vigorous attempt to identify the vulnerabilities to extraction that are peculiar to a specific product. Such vulnerabilities are always relative, in that the active ingredient will eventually be extractable with sufficient time or effort; additional customized tests are thus frequently needed. Intrinsic factors such as the purity of the extract, efficiency of extraction, difficulty of the extraction process, and potency of the extract, as well as extrinsic factors such as price, availability, and access to alternative products¹¹, may all affect the extent to which individuals in the marketplace will attempt to use extraction procedures. The degree to which specific extractability profiles translate into abuse resistance in the real world has not been systematically examined, and is difficult to predict in advance of actual clinical experience; it will likely change with changing conditions.

To be comprehensive, studies that evaluate extractability must include assessments of obvious mechanical manipulations related to the specific product (e.g. removing the gel from a reservoir patch or crushing a tablet), as well as chemical extractability experiments using a battery of

²¹ Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug Alcohol Depend* 2006; 81(2): 103-7.

²² Butler SF, Benoit CM, Budman SH, Fernandez KC, McCormick C, Wing Venuti S, Katz N. Development and validation of an opioid attractiveness scale: a novel measure of the attractiveness of opioid products to potential abusers. *Harm Reduct J*. 2006; 3(1):5.

²³ Laura Nadel, Office of Diversion Control, DEA. Statement before the House Committee on Government Reform: Subcommittee on Criminal Justice, Drug Policy and Human Resources; March 27, 2001. Available at <http://www.usdoj.gov/dea/pubs/cngrtest/ct032701.htm>; Accessed March 5, 2009.

²⁴ Cone EJ. Ephemeral profiles of prescription drug and formulation tampering: evolving pseudoscience on the Internet. *Drug Alcohol Depend*. 2006; 83 Suppl 1:S31-9.

commonly available solvents (including alcohol) tested over a range of temperatures; relevant active comparators must be studied under identical conditions. To the extent possible, study designs for extractability should simulate real-world procedures: for example, tests aimed at examining vulnerability to intravenous injection should use realistic volumes, solvents, needle and syringe sizes, and procedures. Types of extractability experiments will differ with the type of formulation: evaluation of ADFs that are resistant to mechanical or chemical manipulations may focus on resistance to such extraction procedures, whereas assessment of agonist-antagonist formulations may need to focus on the difficulty of separating the antagonist from agonist-containing extracts. Sponsors are encouraged to develop and validate overall metrics of extractability.

Potential advantages conferred by reduced extractability (Table 1, Column 1) include decreased injection, curtailed snorting, lower euphoria or reinforcement produced by the manipulated product, lack of dose dumping or reduced release when co-administered with alcohol, or decreased overall abuse. Since the relevance of various extractability profiles to decreasing actual abuse has not been systematically examined, overall claims about extractability are not, in general, supportable with benchtop studies alone, although descriptions of studies using adequate methodology can be considered for inclusion in the product label. Any clinical benefits of decreased extractability should be demonstrated directly in appropriate clinical or epidemiologic studies.

V b. Claims based on preclinical testing

This section addresses the role of preclinical assays in the development and labeling of opioid analgesics that are assumed or known to have high abuse liability, but that are being developed in an ADF. Preclinical testing can focus on *analgesia* or on *abuse potential*.

Since most ADFs include compounds that are already established analgesics, preclinical studies of analgesia will not, in general, add new information. Exceptions where such testing might be useful include the evaluation of partial agonists or agonist-antagonists for which the therapeutic index is unknown (e.g. the relationship between analgesia and respiratory depression), for which the pharmacokinetics of the new formulation need to be defined, for which the impact of additional actives may influence the analgesic properties of the parent compound, or for which preclinical testing can be used to evaluate proof-of-concept for prodrugs or other products with unique pharmacology. Detailed discussion of the role of preclinical analgesic assays in drug development is beyond the scope of this document.

Preclinical studies for evaluating *abuse potential* fall into three broad groups: drug discrimination, drug self-administration, and drug dependence studies. Below, we further consider such assessments where applicable. In many cases, preclinical studies will likely *not* be informative – they should not be undertaken without clear justification. The following discussion presents situations in which preclinical studies *may* be informative.

Products designed to decrease extractability. Preclinical testing can usefully evaluate the PK of the formulation administered by intended and unintended routes, and under select circumstances can provide a preliminary sense of whether an ADF or its derivative forms (crushed, dissolved, etc.) will be readily bioavailable via alternative routes of administration. An additional role of

preclinical testing of ADFs relates to safety under conditions of abuse. The issue of whether or not improved safety of ADFs for abusers who use altered routes of administration is an important goal of drug development is yet to be resolved. Nonetheless, formulations that produce life-threatening toxicity under conditions of abuse may not achieve their public health goals, and preclinical testing may provide insight into such safety issues.

Agonist/Antagonist Combinations. These products are designed to inactivate the parent opioid upon conditions of tampering, or when the intended route of administration is altered; such an approach generates questions that are usefully addressed by preclinical studies. PK of both parent and antagonist can be explored preclinically, as can the PD effects of exposure to antagonist under conditions that simulate human ingestion via intended and unintended routes: such studies may help in optimizing formulations. Dependence, withdrawal, self-administration, and discrimination studies may help determine the extent to which exposure to antagonist reduces abuse potential.

Aversive formulations. The degree to which exposure to an aversive agent alters self-administration can be explored preclinically; however, the extent to which such studies predict human use is unknown.

Prodrugs. Examples of ADFs of prodrugs include products that are inactive upon intravenous or nasal administration (i.e. they require activation in the gastrointestinal tract), have ceiling effects for respiratory depression due to saturation of the metabolic processes that are required for activation, or have slow onset (for chronic pain). Preclinical studies can be used to explore the PK-PD relationship of these products when administered by intended and unintended routes, and for standard abuse liability assessments.

Drug combinations to diminish abuse potential. The value in reducing abuse potential of the parent compound by adding compounds that selectively block its abuse-related effects can be examined with preclinical abuse potential models.

For all of the above types of formulations and circumstances of abuse, the predictive validity of preclinical models for human abuse is uncertain, making it unlikely that preclinical testing will lead to explicit claims about abuse deterrence. For unusual circumstances in which persuasive evidence exists that preclinical results (e.g. PK) can predict human results, and when such information might be informative to clinicians, description of adequate and well controlled preclinical studies in the product label can be considered.

V c. Claims based on human abuse liability studies

Human abuse liability studies typically consist of multiple-period, complete or incomplete, within-subject crossover designs conducted in small groups of individuals that are experienced in the recreational use of a specific class of drug of abuse. Such studies typically assess whether single doses of active drug, tested at several doses, produce ratings of subjective endpoints assumed to predict real-world drug-taking behavior. However, human abuse liability studies generate surrogate measures that are intended to predict real-world abuse rather than provide actual measurements of real-world abuse; thus explicit claims of abuse deterrence based on such studies are generally not appropriate. Nonetheless, under certain conditions, and pending real-

world assessments of actual abuse, inclusion of such studies in the product label may be considered. Descriptions of human abuse liability studies in the product label, even in the absence of an inference about actual abuse, may provide reliable data to clinicians on the possibility of abuse deterrence; these should be included only if evaluation of actual abuse deterrence in the community is being planned or is ongoing. In other words, inclusion of the description of such a study in the label should be regarded as the first stage of a multi-stage process aimed at generating data to support or refute the implication of the abuse liability assessment; the confirmatory studies would then form the basis on which the appropriateness of continuing to include such descriptions is periodically re-evaluated. For example, a human abuse liability study that demonstrates lower euphoria ratings when an ADF is administered via the intravenous route could be considered for inclusion in the product label. However, continued inclusion of these study results in the label should be contingent on the findings of studies being actively conducted in the community (e.g. large controlled trials, registry studies, epidemiologic studies) to test the hypothesis that, relative to a reference product, the ADF is abused less by the intravenous route.

In determining whether results of a human abuse liability study are appropriate for inclusion in the package insert, the following considerations are important:

- Studies are conducted according to current standards, are typically randomized, are double-blinded, and include a comparator (e.g. placebo) for assay sensitivity.
- The derivative dosage form(s) evaluated (i.e. the “tampered” form of the ADF) are *relevant* to the types of tampering likely to occur.
- Studies demonstrating that one form of tampering yields a derivative dosage form that produces minimal euphoria are not of great value if the product can be readily prepared differently to produce greater euphoria.
- Studies that address common forms of tampering are more relevant than studies to evaluate uncommon forms of tampering.
- Data that support protection against only one form of tampering are incomplete if the product is highly vulnerable to other forms of tampering; in other words, a *comprehensive* battery of such studies, aimed at establishing that one advantage is not negated by other important disadvantages, should be considered for inclusion in the label.
- The reference drug has been carefully selected: for example, a demonstration that an ADF has lower abuse liability than a highly abused reference product, or a product that has been removed from the market, may not be persuasive.
- Outcome measures are *valid* and *reliable*, as with any clinical trial²⁵, with particular reference to predictive validity.
- Differences observed in the clinical trial are not only statistically significant but also have clinical significance²⁶.

²⁵ Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims – Draft Guidance, February 2006. <http://www.fda.gov/CDER/GUIDANCE/5460dft.pdf>. Accessed on March 21, 2009.

²⁶ Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002; 77:371-383.

Examples:

Human liability tests and related labeling statements: Sustained release (SR) oxycodone + capsaicin is being developed as an ADF. Scientific studies designed to provide evidence of abuse deterrence for SR-oxycodone+capsaicin may include: i) human abuse liability studies on the untampered ADF (SR oxycodone+capsaicin vs. reference SR oxycodone), ii) human abuse liability studies on the tampered ADF (chewed SR oxycodone+capsaicin vs. chewed reference product; benchtop test results could direct the specific aspect of the tampered product that is most important to focus on with regard to abuse. The specific design may be affected by PK of the drug/formulation, route of administration (i.e., intravenous, PO, etc.), study population (e.g. opioid-dependent vs. non-dependent), and expertise needed for extraction.

Labeling statement: “Euphoria ratings for SR-oxycodone+capsaicin were lower than for control drug oxycodone SR at doses from x to y mg.”

Labeling statement: “Self administration of SR-oxycodone+capsaicin was lower than for control drug oxycodone SR.”

V d. Claims based on measuring abuse in clinical trials of analgesia

Prescription opioid abuse is a problem among both *patients* (individuals prescribed the medication for appropriate therapeutic indications) and *non-patients* (individuals who are not prescribed the medication but obtain it outside the legitimate prescriber-patient relationship for psychoactive purposes). Rates of abuse can be monitored and, under appropriate conditions, conclusions can potentially be drawn about the relative abuse rate of one product compared to another in clinical trials conducted in patients that require a product for analgesia. Here we discuss several of conditions that must be met in order to draw scientifically valid conclusions from such studies.

An important prerequisite in the design of clinical trials that produce valid results is that the measures used must be relevant. *Construct-related validity* refers to whether a scale used in a study actually measures or correlates with the theorized construct or phenomenon that is intended to be measured²⁵. A first step toward achieving construct-related validity is to clearly spell out the construct that the study is attempting to measure. For instance, the term “abuse” is used inconsistently, and requires a clear and relevant definition for a specific clinical trial: it could be defined as any use of a drug for the purpose of producing euphoria¹⁰, intake of the product by a specific method (crushing and swallowing, or dissolving and injecting), administering the product after any form of tampering, or, according to DSM-IV, as a type of substance use disorder²⁷. Moreover, during a clinical trial, abuse can relate to the prescribed opioid alone, or also to other substances (e.g. cocaine or marijuana).

The choice of construct may not be straightforward and may require certain trade-offs. The construct should be linked to the properties of the product: for example, measuring overall abuse as the primary endpoint for a product that only inhibits one very specific form of abuse (e.g. crushing and snorting) is unlikely to demonstrate benefit; conversely, demonstrating reduced

²⁷ [Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR \(2000\) Fourth Edition \(Text Revision\)](#). American Psychiatric Association.

rates of only a very specific form of abuse, while other forms of abuse are unchanged (or even increased), would have questionable clinical relevance, and therefore questionable relevance for description in a product label.

Once the underlying construct has been defined, the measures employed must relate to this construct, and be fully validated. Currently, there is very limited experience with validation of endpoints for clinical trials that assess abuse liability of opioids in patients with pain, and evidence of validity of any measures chosen must be provided in order to draw valid inferences from the clinical trial. Options have included urine drug monitoring, patient self-report instruments (anonymous or not), observer questionnaires, aberrant behavior checklists, prescription monitoring reports, criminal records, monitoring for specific adverse events, and various composites of the above. The magnitude of a difference between groups on the outcome measure in question must also be clinically important.

Sample size requirements for such trials will depend on the rate of the event in question (e.g., abuse) and on the chosen primary outcome measure, in the population to be studied. Uncommon events require large sample sizes; sample sizes may be smaller when studying populations that are at higher risk for the event of interest (such as patients with previous addiction problems), but the smaller samples then lead to trade-offs in terms of generalizability to lower risk populations. Increased event rates and greater clinical relevance may be achievable with longer duration of follow-up, but also with obvious trade-offs. Descriptions of the results of such studies in product labels, if appropriate, should be focused on the specifics of the population studied and methods employed.

Use of an appropriate *comparator(s)* is important not only to demonstrate a relative reduction in abuse rate, but also to document the absence of any trade-offs in terms of therapeutic effects (e.g. onset, duration, degree of analgesia), safety issues, etc. Utilizing single products as comparators has the advantage of yielding more homogeneous data, but the relevance of the results to a specific product that may or not be marketed in the future are limited, and also leaves unanswered the question of relative abuse liability compared to other therapeutic options.

Difficult ethical considerations may arise in the design of such studies. For example, continuing to prescribe a product to a patient who is known to the study to be abusing that product may not be appropriate. Anonymous outcome data may increase accuracy of reporting, but may not be medically appropriate in all circumstances. Other issues will, no doubt, also arise in the future.

Example:

Measuring abuse in clinical trials of analgesia and related labeling statements: An active controlled (innovator against reformulation) trial of 6 months duration conducted on a population at high risk for diversion or abuse (e.g., chronic pain patients that abuse oxycodone). Exclusion: active addiction. Primary outcome measures may include aberrant behaviors checklist, evidence of diversion/misuse; other measures may include patterns of adverse effect,, results of quantitative urine testing, evidence of tampering, measures of liking, overdoses, and other indicators of drug use. Meaningful differences in outcome between use of innovator vs. reformulation could yield the following:

Labeling statement: “The rate of abuse [as defined in the study] was lower with [ADF] than with [innovator] in a clinical trial of patients with pain [further defined].”

V e. Claims based on Alcohol interactions

Alcohol and prescription opioids interact to produce a number of serious public health consequences. The risk of opioid overdose is thought to be higher in the setting of concomitant alcohol ingestion, which can occur in the context of intentional abuse or therapeutic use of opioids. Concomitant ingestion of alcohol and prescription opioids occurs commonly among victims of opioid poisoning, and is endorsed by approximately 1 in 25 college students per year^{28, 29}. Because of this, package inserts for all prescription opioids warn against co-ingestion of alcohol. The risk of developing alcoholism is higher in prescription opioid addicts than in the general population, and conversely, the potential for developing prescription opioid addiction is greater in alcoholics than in the general population.

Diminishing the impact of alcohol-opioid interactions is therefore a public health goal, and formulation approaches can potentially contribute to a solution. At a minimum, formulations should be designed to not release their active ingredient at an accelerated pace (or “dose dump”) in the context of a concomitant alcohol ingestion³⁰. Additionally, formulations for prescribed opioids can be envisioned that provide added safety by releasing *substantially less* active ingredient in the setting of alcohol co-ingestion than would normally be released, by producing *aversive reactions* to co-ingested alcohol, or via use of other positive forms for deterring co-ingestion of alcohol with the opioid.

The body of evidence to demonstrate that a particular formulation is “alcohol deterrent” recapitulates the five categories of data (see IV above) that can be applied to demonstrate the overall abuse deterrence of a formulation: *in vitro*, preclinical, human pharmacology, analgesic clinical trial, and epidemiology.

Tests of *in vitro* dissolution, as well as of extractability, are critical for establishing interactions of an ADF with alcohol. Correspondence between *in vitro* tests and human pharmacology experiments is inexact³¹, and the potential for an adverse pharmacodynamic interaction exists even in the absence of a pharmacokinetic interaction: removing alcohol warnings from prescription opioid labels will thus not be possible. However, properly designed *in vitro* studies that show absence of dose dumping with alcohol may be considered for the package insert. A labeling statement implying that a product is “alcohol resistant”, or inhibits the release of API in

²⁸ Compton WM, & Volkow ND. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug and Alcohol Dependence* 2006; 81, 103-107.

²⁹ Johnston LD, O'Malley PM, Bachman JG, & Schulenberg JE (2005a). Monitoring the Future National survey results on drug use, 1975-2004. College students and adults ages 19-45, vol. II. Bethesda, MD: National Institute on Drug Abuse (NIH Publication 05-5728). <http://www.drugabuse.gov/PDF/overview2005.pdf>; Accessed February 8, 2009.

30 Walden M, Nicholls FA, Smith KJ, Tucker GT. The effect of ethanol on the release of opioids from oral prolonged-release preparations. *Drug Dev Ind Pharm* 2007; 33(10) 1101-1111.

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the presence of alcohol, should be confirmed with human pharmacology studies (akin to bioequivalence studies) before inclusion in a product label. General principles of implicit vs. explicit labeling for abuse deterrence would also apply to "alcohol deterrence" in all cases.

Examples:

Labeling statement: *"In vitro tests demonstrate that there is no acceleration of release of active ingredient from Product X when dissolved in concentrations of ethanol ranging from 0-100%."*

Labeling statement: *"In vitro tests demonstrate that there is inhibition of release of active ingredient from Product Y when dissolved in concentrations of ethanol ranging from 4-100%, with a maximum of 50% of label claim released in the first two hours of dissolution."*

The study of alcohol interactions in human clinical pharmacology experiments may be complex, with assessments of bioequivalence (with and without alcohol; fasted subjects, 240 ml of 40% ethanol, within 15 minutes of ingestion) needed for each active constituent in the ADF. Interpretation of such studies is limited by a number of factors, including, but not limited to, the following: (i) clinical relevance of plasma concentrations of either ethanol or opioids is subject to wide variability, and pharmacodynamic endpoints, such as markers of respiratory depression, are generally necessary to establish such relevance; (ii) for either pharmacokinetic or pharmacodynamic endpoints, shifts in group means of may be less relevant than the proportion of "outliers"; study endpoints should thus explicitly assess the proportion of individuals meeting clinically meaningful safety endpoints; (iii) in pharmacology studies, clinical relevance of the endpoints for predicting population effects is generally unknown; therefore justification must be provided for the clinical relevance of any endpoints; and (iv) the clinical relevance of study conditions (amount of alcohol, amount of opioid, etc.) must be relevant to the risk situation that the study is attempting to illuminate. Despite these methodological challenges, however, results of human pharmacology studies that are carefully designed and conducted can be considered for description in the package insert.

Example:

Labeling statement: *"A human clinical study of alcohol interaction study was conducted in order to compare Product X to equivalent doses of a reference extended-release oxycodone product, under test conditions that involved co-ingestion with 240ml of 4, 20, 40, and 100% ethanol. Plasma concentrations of active ingredient, and pharmacodynamic endpoints indicative of potential respiratory depression, were statistically and clinically lower with Product X. See Table for details."*

As for all ADFs, "real world" clinical data are ultimately required to understand the relevance of findings from *in vitro*, preclinical, or human pharmacology experiments. Consideration may be given to large clinical trials of individuals at risk for negative health events from concomitant ingestion of alcohol and prescription opioids, with full consideration of subject safety and other ethical and scientific issues as discussed above. Epidemiologic studies are likely to be ultimately required to fully understand the impact of an "alcohol resistant" formulation.

Example:

Labeling statement: *“In a large registry study of patients with chronic pain who were prescribed various opioids, patients prescribed Product X experienced a statistically and clinically significantly lower incidence of events attributed to alcohol-opioid co-ingestion compared to a group of reference products, adjusted for baseline risk of such events. See Table for details.”*

V f. Claims based on Epidemiological Studies

Most prescription opioid abuse appears to occur among individuals who are not patients, i.e. they have not received their opioids from a prescriber for therapeutic purposes; thus clinical trials for pain alone cannot fully assess abuse. Epidemiologic studies are needed to provide an overall picture of the abuse of a product. Furthermore, patient registries, claims studies, and other clinical studies considered to be epidemiologic studies, may provide a fuller picture even of abuse among patients than can be derived from clinical trials alone. A complete picture of the abuse of a specific product thus requires epidemiologic studies as a prerequisite for any explicit claim about abuse-deterrence. Moreover, since each type of study will have limitations, it is likely that several types of studies, each complementing the flaws of the others, will be necessary to provide a valid and robust picture of the abuse of a specific prescription opioid.

Most conditions needed for a valid clinical trial [section V d] also apply to epidemiologic studies, as do a variety of methodological issues. A major challenge is how to address *confounding by indication*; in other words, when individuals are non-randomly assigned to treatment, patients may be unequally distributed for factors that relate to the outcome of interest, thus biasing results. And in population-based studies, the *environmental fallacy* must also be addressed, namely that regional availability of a specific product may not equate to availability to an individual; these are but two examples; design of epidemiologic studies should be done with appropriate expert input. Bearing these issues in mind several types of label statements can be considered.

Examples:

Labeling statement: *“Product X has been shown to be associated with lower prevalence of abuse[define] in a population-based study than other formulations containing the same active ingredient(s).”*

Labeling statement: *“Product X has been shown to be associated with lower prevalence of [route of administration] abuse than other formulations containing the same active ingredient(s).”*

The design of post-approval patient studies to support these labels should include appropriate active comparators, indicators of abuse/addiction, indicators of diversion, active safety surveillance (including incidence of adverse effects), and surveillance of active effectiveness. Patient stratification according to known risk factors for abuse and co-morbidities, along with condition-based (rather than only product-based) Registry studies, may also be informative; these should be designed according to existing FDA guidelines.

V g. Miscellaneous claims

In certain cases labeling statements may not flow from a specific category of evidence, but may nevertheless be based on the extent to which the product deters abuse. Companies should be

alerted to specific parts of the label that can be modified according to unique properties of the new formulation. The following types of information that may be included in the Package insert:

- For agonist/antagonist combination (in Clinical Pharmacology section): *Summary of PK studies showing bioavailability - or lack thereof - of antagonist by oral route), studies to demonstrate bioavailability of antagonist by intranasal route (after crushing).*
- For agonist/antagonist combination (in Animal Pharmacology/Toxicology section): *Summary of non-clinical studies to support dose of antagonist that would precipitate withdrawal.*

Examples:

Labeling statement for agonist/antagonist combination (in CMC – Description section): “*An opiate antagonist [name] has been added to this formulation in an attempt to deter abuse by the intravenous route.*”

Labeling statement (in Warning section) “***WARNING. This product should only be administered orally. It contains an opiate antagonist which, if administered intravenously (or intranasally) may precipitate opiate withdrawal.***”

VI. PROCESS ISSUES

A timeline for the key regulatory interactions during drug development is presented in Table 2. Comments are provided with respect to the role of each meeting in contributing towards the ultimate inclusion of evidence-based labeling language related to abuse deterrence in the product label.

Table 2: Timeline for key regulatory interactions

Meeting	Objective	Comments
Pre-IND	<ul style="list-style-type: none"> • Discuss product strategy • Early regulatory input 	<ul style="list-style-type: none"> • Understand product development strategy • Rudimentary discussion of labeling plan for appropriateness of studies
EOP-2	<ul style="list-style-type: none"> • Track progress • Develop future plans 	<ul style="list-style-type: none"> • Discuss progress against development hurdles • Phase 3 protocol development, validity of endpoints and designs, labeling criteria, possible SPA
Mid-Phase III	<ul style="list-style-type: none"> • Discuss challenges • Refine studies 	<ul style="list-style-type: none"> • Review data and discuss deviations from original plan, discuss implementation issues • Implications of changing scientific or public health realities
Pre-NDA	<ul style="list-style-type: none"> • Discuss data • Submission criteria 	<ul style="list-style-type: none"> • Broad overview of trial results, assessment of data appropriateness and quality • Review proposed labeling language against study results • Clarify format and readiness of application • Request Fast Track or Priority Review status • Feedback on REMS and the design of post-marketing studies
Post-marketing/REMS*	<ul style="list-style-type: none"> • Review REMS • Review post-marketing studies for labeling 	<ul style="list-style-type: none"> • Review detailed design of post-marketing studies with intended labeling language • Review results of such studies and final proposed labeling language

*Series of meetings.

EOP2: End of Phase 2; NDA: New Drug Approval; REMS: Risk Evaluation and Mitigation Strategy; SPA: special protocol assessment.

Expediency in identifying and resolving problems during the development process is critically dependent on an open dialog between the FDA and industry sponsors. Clarity of communication between FDA and sponsors will be particularly important in the area of ADFs, where the scientific issues are rapidly evolving, as are clinical realities that impact study design and interpretation. A number of specific implications for ADFs can be gleaned from Table 2. FDA has committed to considering Fast Track or Priority Review status to formulations with the potential to deter abuse, and this should be considered routinely for such products. Also, labeling claims for ADFs will rely to a great extent on studies that may be conducted in the post-marketing arena. Opportunities exist pre-NDA for agreeing on Phase IIIb or Phase IV studies that are designed to support abuse-deterrent labeling, that can be proposed under the umbrella of enforceable REMS obligations, and that may be reviewed post-marketing in the context of required REMS-related meetings.

VII. SUMMARY

This background paper offers a blueprint for initiating a meaningful dialog between the FDA and industry sponsors, in order to facilitate commercialization of new formulations that are targeted towards reducing the scourge of POA.

APPENDIX I

List of participants at the Tufts Health Care Institute Meeting on Abuse Deterrent Formulations, November 2006.

Note that information included in this Background paper is substantively different from the meeting presentations and from the discussions that took place at the conference break-out sections. Individual conference participants, program partner and program supporters are not responsible for specific points included in this paper.

Conference Conveners

Marc M. Edelstein, MD, PhD,
Chief Medical Officer and Co-Director,
Tufts Health Care Institute and
Office of Continuing Education,
136 Harrison Avenue,
Boston, MA 02111.
Tel: 617-636-0347
Fax: 617-636-0429
Marc_Edelstein@tufts-health.com

Nathaniel Katz, MD, MS
Adjunct Assistant Professor,
Master of Science in Pain Research,
Education and Policy,
Adjunct Professor of Anesthesiology,
Tufts University School of Medicine,
Analgesic Research,
109 Highland Avenue,
Needham, MA 02494.
Main: 781-444-9605
Fax: 617-663-6287
nkatz@analgesicresearch.com

Invited Participants

Edgar H. Adams, ScD,
Executive Director, Epidemiology,
Late Stage Development Services,
Covance,
210 Carnegie Center,
Princeton, NJ 08540-6233.
Tel: 609-452-4827
Edgar.adams@covance.com

Edward J. Cone, PhD,
ConeChem Research, LLC,
441 Fairtree Drive,
Severna Park, MD 21146.
Tel: 410-315-8643
Fax: 410-315-9067
econe@pinneyassociates.com

edward.cone@comcast.net

Don Cooper,
PO Box 396,
Purcellville, VA 20132.
Tel: 540-338-3049
doncooper@cooperandcompany.com

Richard A. Denisco, MD, MPH,
Health Scientist Administrator,
Services Research Branch,
Division of Epidemiology, Services and Prevention Research,
National Institute on Drug Abuse,
6001 Executive Boulevard,
Room 5185, MSC 9589,
Bethesda, MD 20892-9589.
Tel: 301-594-4371
Fax: 301-443-6815
deniscor@nida.nih.gov

William L. Dewey, PhD,
Virginia Commonwealth University,
Dept. of Pharmacology and Toxicology,
PO Box 980613, MCV Station,
Richmond, VA 23298-0613.
Tel. (804) 827-0375
wdewey@hsc.vcu.edu

Richard W. Foltin, PhD,
Professor of Neuroscience, Department of Psychiatry,
College of Physicians and Surgeons of Columbia University,
1051 Riverside Drive,
Unit 120,
New York, NY 10032.
Phone: 212-543-5717
Fax: 212-543-5991
rwf2@pop.columbia.edu

Philip Goliber, PhD,
Vice President, Pharmaceutical R&D,
Penwest Pharmaceuticals Company,
2981 Route 22,
Suite 2,
Patterson, NY.
Tel: 845 878-8402
Fax: 845 878-3420
Phil.goliber@penwest.com

Louis S. Harris, PhD,
Medical College of Virginia-VCU,
Pharmacology & Toxicology,
1112 E. Clay Street,
Room 332,
Richmond, VA 23298-0027.

Tel: (804) 828-2075
harris@hsc.vcu.edu

Donald Jasinski, MD,
Professor of Medicine,
Chief, Center for Chemical Dependence,
Johns Hopkins Bayview Medical Center,
Mason F. Lord Building,
West Tower, 2nd Floor,
4940 Eastern Avenue,
Baltimore, Maryland 21224.
Tel: 410-550-1906
Fax: 410-550-1912
drjasins@jhmi.edu

Chris-Ellyn Johanson, PhD,
Department of Psychiatry,
Loyola University Chicago,
Stritch School of Medicine,
2160 S First Avenue,
Building 105, Room 1940,
Maywood, IL 60153.
cjohans@med.wayne.edu

E. Douglas Kramer, MD,
Associate Director,
CNS Clinical Research,
Schering Plough Research Institute,
2015 Galloping Hill Road,
K-15-3-3300,
Kenilworth, NJ 07033-1300.
Tel: 908-740-5868
Doug.kramer@spcorp.com

Cynthia McCormick, MD,
McCormick Consultation, LLC,
9127 Friars Road,
Bethesda, MD 20817.
Tel: 301-564-4049
Fax: 301-564-0151
cgmc@comcast.net

S. Stevens Negus, PhD,
Harvard Medical School,
Department of Psychiatry,
Alcohol and Drug Abuse Research Center, McLean Hospital,
115 Mill Street,
Belmont, MA 02478.
Tel. 617-855-3324
negus@mclean.harvard.edu

Jennifer Sharpe Potter, PhD, MPH,
Instructor in Psychology, Harvard Medical School,
Research Director, Alcohol & Drug Abuse Treatment Program,
McLean Hospital, Proctor House,

115 Mill Street,
Belmont, MA 02478.
Tel: 617-855-3215
Fax: 617-855-2699
jpotter@mclean.harvard.edu

Bruce Rounsaville, MD,
Professor of Psychiatry,
Yale University School of Medicine,
Director, Mental Illness Research Education and Clinical Center,
U.S. Veterans Administration,
950 Campbell Avenue (151D),
West Haven, CT 06516.
Tel: 203 932 5711 x 7401
Fax: 203 937 3869
Bruce.Rounsaville@yale.edu

Seddon R. Savage MS, MD,
Director, Dartmouth Center on Addiction Recovery and Education (DCARE),
Pain Consultant, Manchester VA Medical Center,
Associate Prof Anesthesiology, Dartmouth Medical School, Adjunct Faculty,
40 College Street,
Hanover, NH 03755.
Tel: 603-646-9215
Fax: 603-646-9151
Seddon.R.Savage@Dartmouth.edu

William K. Schmidt, PhD,
NorthStar Consulting, LLC,
1337 Marina Circle,
Davis, CA 95616.
Tel: 650-438-3018
Fax: 866-410-8835
schmidtwk@sbcglobal.net

Sidney H. Schnoll, MD, PhD,
Medical College of Virginia,
Columbia University,
2 Beachside Common,
Westport, CT 06880.
Tel: 203-341-9458
Fax: 203-341-9571
sidschnoll@mindspring.com

Edward Sellers, MD, PhD, FRCPC,
President and CEO,
Ventana Clinical Research Corporation,
720 King Street W, 7th Floor,
Toronto, ON M5V 2T3.
Tel: 416-963-5602 x440
Fax: 416-963-9732
e.sellers@ventana-crc.com

Beatrice Setnik, PhD,
Research Scientist,

Ventana Clinical Research Corporation,
720 King Street West, Suite 700,
Toronto, Ontario M5V-2T3.
Tel: 416.963.5602 Ext. 323 Fax: 416.963.9732
b.setnik@ventana-crc.com

Eric C. Strain, MD,
Professor, Medical Director, Behavioral Pharmacology Research Unit,
Department of Psychiatry and Behavioral Sciences,
Johns Hopkins University School of Medicine,
5510 Nathan Shock Drive,
Baltimore, MD 21224.
Tel: 410-550-1191
Fax: 410-550-0030
ECSGSS@aol.com

Sharon L. Walsh, PhD,
Professor of Behavioral Science,
Executive Director Center on Drug and Alcohol Research,
University of Kentucky,
515 Oldham Court,
Lexington, KY 40502.
Tel: 859-257-6485
Alt. Tel: 859-323-6126
Fax: 859-257-5232
Sharon.walsh@uky.edu

James P. Zacny, PhD,
Department of Anesthesia & Critical Care,
MC4028, University of Chicago,
5841 S Maryland Avenue,
Chicago, IL 60637.
Tel: 773-702-9920
Fax: 773-702-6179
JZacny@dacc.uchicago.edu

Tufts Health Care Institute

Marc Edelstein, MD, PhD,
CMO and Co-director, Tufts Health Care Institute,
Tufts University Office of Continuing Education,
136 Harrison Avenue,
Boston, MA 02111.
Tel: 617-636-0347
Fax: 617-636-0429
Marc_Edelstein@tufts-health.com

Ralph Halpern,
Director, Content Development and Program Evaluation,
Tufts Health Care Institute,
136 Harrison Avenue,
Boston, MA 02111.
Tel: 617-636-3991

Fax: 617-636-0429
Ralph_Halpern@tufts-health.com

Kathleen Lowney, MHA,
Director, Administration and Operations,
Tufts Health Care Institute and Tufts University Office of Continuing Education,
136 Harrison Avenue,
Boston, MA 02111.
Tel: 617-636-3789
Fax: 617-636-0429
Kathleen.Lowney@tufts.edu

Deborah Morris, MBA,
Director, Finance and Planning,
Tufts Health Care Institute,
136 Harrison Avenue,
Boston, MA 02111.
Tel: 617-636-2950
Fax: 617-636-0429
Deborah_morris@tufts-health.com

Rosalie Phillips, MPH,
Executive Director,
Tufts Health Care Institute,
Co-director, Tufts University Office of Continuing Education,
136 Harrison Avenue,
Boston, MA 02111.
Tel: 617-636-1000
Fax: 617-636-0429
Rosalie_Phillips@tufts-health.com

Program Partners

King Pharmaceuticals

John LaLota
Senior Vice-President, Neuroscience Marketing,
King Pharmaceuticals®, Inc.,
400 Crossing Blvd. - 7th Floor,
Bridgewater, NJ 08807.
Tel: 908-429-6000 ext. 58050
Fax: 423-274-2518

Carl L. Roland, PharmD,
Director, Clinical Research,
King Pharmaceuticals R&D,
4000 Centre Green Way, Suite 300,
Cary, NC 27513.
Tel: 919-653-7011

Purdue

J. David Haddox, DDS, MD,
Vice President, Risk Management and Health Policy,
One Stamford Forum,
Stamford, CT 06901-3431.
Tel: 203-588-7667
Fax: 203-588-6242
Dr.J.David.Haddox@pharma.com

Judy Lee, MD,
Sr. Director, Analytics/Preformulation,
Discovery Research Facility,
6 Cedarbrook Drive,
Cranbury, NJ 08512.
Tel: 609-409-5126
Cell: 973-723-4782

Program Supporters

Abbott

Michael A Jones,
General Manager,
Pharmaceutical Products,
Pain Care Franchise,
200 Abbott Park Road,
Dept 096K Bldg AP30,
Abbott Park, IL 60064-6182.
Tel: 847-937-9146
Fax 847-938-7963
Mike.A.Jones@abbott.com

Earle Lockhart, MD,
Medical Director,
Abbott Pain Care,
200 Abbott Park Road,
Dept. R440, AP34-1,
Abbott Park, IL 60064-6182.
Tel: 847-938-1076
Fax: 847-935-7633
earle.lockhart@abbott.com

Alpharma

Joseph Stauffer, DO,
Vice President, Global Medical Affairs,
1 New England Avenue,
Piscataway, NJ 08854.
Tel: 732-465-3636
Fax: 732-465-3730
Joe.stauffer@alpharma.com

Ron Warner, PhD,
President,
1 New England Avenue,
Piscataway, NJ 08854.
Ronald.Warner@Alpharma.com.

Johnson & Johnson

Janet Tamada, PhD,
Research Fellow/Director, Early Development,
ALZA Corporation,
1900 Charleston Road,
Mountainview, CA 94043.
Tel: 650-564-7049
Fax: 650-564-2484
jtamada@alzus.jnj.com

John Thippawong, MD,
Senior Director, Clinical Development,
1950 Charleston Road,
Mountainview, CA 94043.
Tel. 650-564-5196
Fax 650-564-2033
JThippa@ALZUS.JNJ.COM

Endo Pharmaceuticals

Robert F. Reder, MD,
VP, Clinical R&D/Senior Medical Officer,
100 Endo Boulevard,
Chadds Ford, PA 19317.
Tel: 610-558-9800 Ext 4037
Reder.robert@endo.com

Grunenthal

Stephan Buller,
Department of Clinical Pharmacology,
Grunenthal GmbH,
52099 Aachen,
Germany.
+49 241-569-2126

Silvia Dickhut,
Department of New Therapeutic Entities,
Grunenthal GmbH,
52099 Aachen,
Germany.
+49 241-569-2514

Pain Therapeutics, Inc.

Steve Johnson,
Executive Director, Commercial Planning,
Pain Therapeutics, Incorporated,
416 Browning Way,
South San Francisco, CA 94080.
Tel: 650-825-3331
Cell: 415-250-7428
Fax: 650- 624-8222
sjohnson@paintrials.com

Michael S. Zamloot,
Senior Vice President, Technical Operations,
Pain Therapeutics, Incorporated,
416 Browning Way,
South San Francisco, CA 94080.
Tel: 650-825-3340
Cell: 650-245-6715
Fax: 650- 624-8222
mzamloot@paintrials.com