

# Conference Welcome

The College on Problems of Drug Dependence, Inc. (CPDD), formerly the Committee on Problems of Drug Dependence, has existed since 1929 and is the longest standing group in the United States addressing problems of drug dependence and abuse. CPDD serves as an interface among governmental, industrial, and academic communities, maintaining liaisons with regulatory and research agencies as well as with educational, treatment, and prevention facilities in the drug abuse field. CPDD is a collaborating center of the World Health Organization.

CPDD has played a leading role in advancing research methodology and in evaluating drugs with abuse potential. In October 2001, CPDD sponsored the meeting “Abuse Liability Assessment on CNS Drugs.” The papers from that meeting were published in *Drug and Alcohol Dependence*, Volume 70, Issue 3, Supplement 1, June 2003. Among the recommendations from the meeting were that more attention should be paid to evaluating the impact of formulations on abuse liability. Developing methodologies to study new formulations was identified as a particular need of the field.

In light of recent increased publicity concerning diversion and the issue of tampering with prescription medication, new formulations are being widely considered as a strategy to reduce risk. These approaches are occurring in a context where regulatory, law enforcement, and research frameworks have not been fully developed to accommodate these new formulations. Importantly, there are few epidemiologic data as to the impact of formulation on the public health risk for abuse of prescription medications.

This meeting begins to address these issues and will develop a research agenda for the field. The program includes invited presentations and submitted original research papers. All submitted abstracts were reviewed by the Conference Program Committee before acceptance. Papers based on the invited presentation and abstracts will be published in a supplement of *Drug and Alcohol Dependence* later this year, along with the conclusions from the conference. Our hope is that the proceedings of this meeting will contribute to the consideration of the research, regulatory, and public health issues raised by the development of new formulations designed to reduce the diversion and abuse of medications.

On behalf of CPDD, we would like to express our thanks to the Conference Program Committee and the meeting sponsors listed in the program for their financial support and interest. These sponsors have given unrestricted, educational funds to CPDD for this meeting. The planning of this meeting has been an opportunity to hear many different and helpful perspectives.

Edward M. Sellers, M.D., Ph.D., Chair

Charles R. Schuster, Ph.D., Co-Chair

April 19, 2005

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## *Drug and Alcohol Dependence Supplement*

Meeting Manuscripts and Abstracts

### **Managing Editor**

Robert L. Balster, Ph.D.

### **Invited Editors**

Edward M. Sellers, M.D., Ph.D.  
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# Conference Program

Day 1: April 19, 2005

7:30 – 8:30 a.m.

**Breakfast**  
*White Flint Amphitheater*

8:30 – 8:45 a.m.

**Introduction/Welcome**  
*Edward M. Sellers, M.D., Ph.D.*  
*Ventana Clinical Research Corporation*  
*University of Toronto*

## **Invited Speaker Presentations**

*White Flint Amphitheater*

8:45 – 9:15 a.m.

**Priorities in Prescription Drug Abuse Research**  
*Nora D. Volkow, M.D.*  
*Director*  
*National Institute on Drug Abuse*

9:15 – 9:45 a.m.

**History and Current Perspectives on the Use of Drug Formulations to Decrease the Abuse of Prescription Drugs**  
*Charles R. Schuster, Ph.D.*  
*Substance Abuse Clinical Research Division*  
*Department of Psychiatry and Behavioral Neurosciences*  
*Wayne State University School of Medicine*

9:45 – 10:15 a.m.

**Prescription Drugs and the Risks of Abuse, Addiction, and Overdose: Regulatory Challenges**  
*Deborah B. Leiderman, M.D., M.A.*  
*Director*  
*Controlled Substance Staff*  
*Office of the Center Director*  
*Center for Drug Evaluation and Research*  
*Food and Drug Administration*

10:15 – 10:30 a.m.

**Break**

10:30 – 11:00 a.m.

**Influence of Formulation on the Development of Medications with Abuse Potential**  
*Robert S. Mansbach, Ph.D.*  
*Director*  
*Program Management and Regulatory Science*  
*Neurocrine Biosciences*

11:00 – 11:30 a.m.

**Abuse Resistant Formulations and the Controlled Substances Act**  
*Frank L. Sapienza, M.S.*  
*Drug & Chemical Advisory Group, LLC*

11:30 a.m. – 12:00 noon

**Ephemeral Profiles of Prescription Drug Tampering: Evolving Pseudoscience on the Internet**  
*Edward J. Cone, Ph.D.*  
*ConeChem Research, LLC*

12:00 noon – 12:30 p.m.

**Premeeting Survey of the Views Held by the Conference Participants**  
*Charles Grudzinskas, Ph.D.*  
*Principal*  
*NDA Partners, LLC*  
*Center for Drug Development Science*  
*University of California, San Francisco*

12:30 – 1:30 p.m.

**Lunch**  
*Salon C*

## Submitted Presentations

*Theme: From the Street to the Lab and Back*

- 1:30 – 1:45 p.m.**                    **Surrogate Manipulations of Drug Kinetics and How They Affect the Abuse Potential of Drugs Using Nonhuman Primates**  
*Robert L. Balster, Ph.D.*  
*Director*  
*Institute for Drug and Alcohol Studies*  
*Butler Professor of Pharmacology and Toxicology*  
*Virginia Commonwealth University*
- 1:45 – 2:00 p.m.**                    **Benchtop Testing of Opioid Formulations for Tamper Liability**  
*Philip A. Goliber, Ph.D.*  
*Senior Director*  
*Purdue Pharma, LP*
- 2:00 – 2:15 p.m.**                    **A Novel Technology for Dispensing and Monitoring Controlled Substances in Research and Therapeutics**  
*Geoffrey W. Guy, M.D.*  
*Executive Chairman*  
*GW Pharmaceuticals, PLC*
- 2:15 – 2:30 p.m.**                    **Relative Abuse Liability of Opioid Dosage Forms in Canada: Assessing the Potential for Tampering**  
*Marjie L. Hard, Ph.D.*  
*Research Scientist*  
*Ventana Clinical Research Corporation*
- 2:30 – 2:45 p.m.**                    **A New Technology to Increase the Mechanical Stability of Matrix Tablets to Prevent Abuse by Crushing or Chewing**  
*Judy B. Ashworth, M.D.*  
*International Project Manager*  
*Grunenthal GmbH*
- 2:45 – 3:00 p.m.**                    **Break**

## Invited Speaker Presentation

- 3:00 – 3:30 p.m.**                    **The Development of Opioid Formulations with Limited Diversion and Abuse Potential**  
*Paul J. Fudala, Ph.D., R.Ph.*  
*Supervisory Toxicologist*  
*Philadelphia VA Medical Center*  
*Research Associate Professor of Pharmacology in Psychiatry*  
*University of Pennsylvania School of Medicine*

## Submitted Presentations

*Theme: Formulation Opiate Agonists, Partial Agonists, and Antagonists*

- 3:30 – 3:45 p.m.**                    **Adding Naloxone to Opioids to Decrease Abuse Potential: Rationale, History, and Evidence of Efficacy**  
*Eric C. Strain, M.D.*  
*Professor*  
*Department of Psychiatry and Behavioral Science*  
*Johns Hopkins University*
- 3:45 – 4:00 p.m.**                    **Abuse Liability of Intravenous Buprenorphine, the Buprenorphine/Naloxone Combination, and Methadone in Recently Detoxified Heroin Abusers**  
*Sandra D. Comer, Ph.D.*  
*Associate Professor*  
*Columbia University*
- 4:00 – 4:15 p.m.**                    **Phase 1 Testing of Opioid Agonist-Antagonist Formulations in Man**  
*Stephen C. Harris, M.D.*  
*Medical Director*  
*Purdue Pharma, LP*

## Submitted Presentations

*Theme: New Products*

**4:15 – 4:30 p.m.**

### **Ultra-Low-Dose Naltrexone Reduces Addictive Potential of Oxycodone in Rats**

*Lindsay H. Burns, Ph.D.*

*Director*

*Preclinical Research*

*Pain Therapeutics, Inc.*

**4:30 – 4:45 p.m.**

### **A Novel, Long-Acting Oxycodone Formulation Deters Abuse in Humans**

*Nadav Friedmann, Ph.D., M.D.*

*Chief Operating and Medical Officer*

*Pain Therapeutics, Inc.*

**4:45 – 5:00 p.m.**

### **Methylphenidate Transdermal System for the Treatment of ADHD**

*Geoffrey A. Dugue, M.D., M.P.H.*

*Director*

*Clinical Research*

*Noven Pharmaceuticals, Inc.*

**5:00 – 5:15 p.m.**

### **Novel 6-Month Buprenorphine Dosage Form for Treatment of Opioid Dependence**

*Lauren C. Costantini, Ph.D.*

*Director*

*Product Development*

*Titan Pharmaceuticals, Inc.*

**5:15 – 5:30 p.m.**

### **The Impact of Abuse Deterrent Formulation on the Incidence of Abuse and Diversion of OROS® Methylphenidate**

*Robert L. DuPont, M.D.*

*Chair*

*Prescription Drug Research Center*

**5:30 – 5:45 p.m.**

### **The Question of Tolerance: Cannabis-Based Medicine Provides Long-Term Clinical Efficacy without Dosage Increases or Withdrawal**

*Geoffrey W. Guy, M.D.*

**5:45 p.m.**

***End of Session***

**5:45 – 7:00 p.m.**

***Reception***

*Salons G and H*

*Chair, Edward M. Sellers, M.D., Ph.D.*

*Co-Chair, Charles R. Schuster, Ph.D.*

# Conference Program

Day 2: April 20, 2005

7:30 – 8:30 a.m.

**Breakfast**  
*White Flint Amphitheater*

## **Invited Speaker Presentations**

*White Flint Amphitheater*

8:30 – 9:00 a.m.

**Exempt Preparations: Historical Perspectives**  
*Louis S. Harris, Ph.D.*  
*Harvey Haag Professor and Vice Chair*  
*Department of Pharmacology and Toxicology*  
*Medical College of Virginia*  
*Virginia Commonwealth University*

9:00 – 9:30 a.m.

**Research Design Strategies to Evaluate the Impact of Formulation on Abuse Liability**  
*Edward M. Sellers, M.D., Ph.D.*

9:30 – 10:00 a.m.

**Regulatory Challenges for New Formulations in Today's Environment**  
*Cynthia G. McCormick, M.D.*  
*Regulatory Consultant*  
*McCormick Consultation, LLC*

10:00 – 10:15 a.m.

**Break**

10:15 – 10:45 a.m.

**Risk Identification, Risk Assessment, and Risk Management of Abusable Drug Formulations**  
*Curtis Wright IV, M.D., M.P.H.*  
*Executive Medical Director*  
*Purdue Pharma, LP*

## **Submitted Presentations**

*Theme: Risk Identification, Assessment, and Management*

10:45 – 11:00 a.m.

**Risk Management Action Plans for Opioids Now and in the Future**  
*Edgar H. Adams, Sc.D.*  
*President*  
*E. Adams Consulting*

11:00 – 11:15 a.m.

**Research Issues and Experiences in Studying Prescription Drug Diversion**  
*James A. Inciardi, Ph.D.*  
*Professor*  
*Center for Drug and Alcohol Studies*  
*University of Delaware Research Center*

11:15 – 11:30 a.m.

**Measuring Rates of Nonmedical Use—Dimensions and Denominators**  
*Meredith Y. Smith, Ph.D., M.P.A.*  
*Associate Director*  
*Risk Management*  
*Purdue Pharma, LP*

11:30 – 11:45 a.m.

**The Standards for Risk Management Plans for High Abuse Potential Medications**  
*J. David Haddox, D.D.S., M.D.*  
*Vice President*  
*Risk Management and Health Policy*  
*Purdue Pharma, LP*

11:45 a.m. – 12:00 noon

**Risk Management Solutions for New Drug Formulations: Path to More Flexible CSA Scheduling Options?**  
*Jack E. Henningfield, Ph.D.*  
*Pinney Associates, Inc.*

12:00 noon – 1:00 p.m.	<b>Lunch</b> <i>Salon C</i>
1:00 – 3:00 p.m.	<b>Breakout Sessions</b> <b>Group 1—Regulatory Issues</b> Great Falls <i>Cynthia G. McCormick, M.D.</i> <b>Group 2—Research Needs and Design: Preclinical/In Vitro</b> Linden Oaks <i>Robert L. Balster, Ph.D.</i> <b>Group 3—Risk Management: Assessing Risk</b> Middlebrook <i>Curtis Wright IV, M.D., M.P.H.</i> <b>Group 4—Risk Management: Interventions</b> Oakley <i>Jack E. Henningfield, Ph.D.</i> <b>Group 5—Research Needs and Design: Clinical</b> Brookside A <i>Roland R. Griffiths, Ph.D.</i> <i>Professor</i> <i>Department of Psychiatry and Neuroscience</i> <i>Johns Hopkins University School of Medicine</i> <b>Group 6—New Products</b> Brookside B <i>Robert S. Mansbach, Ph.D.</i>
3:00 – 3:15 p.m.	<b>Break</b>
<b>Presentation of Recommendations</b> <i>White Flint Amphitheater</i>	
3:15 – 3:30 p.m.	<b>Group 1—Regulatory Issues</b> <i>Cynthia G. McCormick, M.D.</i>
3:30 – 3:45 p.m.	<b>Group 2—Research Needs and Design: Preclinical/In Vitro</b> <i>Robert L. Balster, Ph.D.</i>
3:45 – 4:00 p.m.	<b>Group 3—Risk Management: Assessing Risk</b> <i>Curtis Wright IV, M.D., M.P.H.</i>
4:00 – 4:15 p.m.	<b>Group 4—Risk Management: Interventions</b> <i>Jack E. Henningfield, Ph.D.</i>
4:15 – 4:30 p.m.	<b>Group 5—Research Needs and Design: Clinical</b> <i>Roland R. Griffiths, Ph.D.</i>
4:30 – 4:45 p.m.	<b>Group 6—New Products</b> <i>Robert S. Mansbach, Ph.D.</i>
4:45 – 5:15 p.m.	<b>Expert Committee: Discussion, Conclusions, and Recommendations</b> <i>Charles Grudzinkas, Ph.D.</i> <i>Chair, Expert Committee</i>
5:15 – 5:30 p.m.	<b>Concluding Remarks</b> <i>Edward M. Sellers, M.D., Ph.D.</i> <i>Charles R. Schuster, Ph.D.</i>
5:30 p.m.	<b>Adjournment</b>

# Abstracts

Day 1: April 19, 2005

## ***Priorities in Prescription Drug Abuse Research***

*Presenter: Nora D. Volkow, M.D.*

*Director, National Institute on Drug Abuse*

The substantive content of Dr. Volkow's presentation is a U.S. Government work not subject to copyright.

## ***History and Current Perspectives on the Use of Drug Formulations to Decrease the Abuse of Prescription Drugs***

*Presenter: Charles R. Schuster, Ph.D.*

Charles R. Schuster, Ph.D.

Wayne State University School of Medicine

The misuse, abuse and addiction to prescribed medications are not new problems. The prevalence of iatrogenic dependence on injected morphine and cocaine was extremely high in the United States in the 19<sup>th</sup> century. Further, the abuse of patent medicines containing morphine, cocaine and alcohol was widespread. The recognition of these problems around the turn of the century led to the passage of the Pure Food and Drug Act (1906) and the Harrison Narcotic Act (1914). Although this legislation decreased the abuse of medications, it remained a significant problem that has increased in the past several years. The historical roots of the College on Problems of Drug Dependence as an organization devoted to discovering analgesic medications with the efficacy of opiates but without their abuse potential will be reviewed. An alternative approach has been to develop formulations that combine drugs with abuse potential with secondary ingredients that decrease their likelihood of abuse. The combination of the opiate diphenoxylate and atropine for the treatment of diarrhea is an example of this type of formulation. New formulations are also being developed based upon research that has shown that the rate of onset and offset of drugs of abuse is an important variable in their abuse potential. Formulations that slow the rate of onset and offset of the drugs effects would be predicted to have lower abuse potential. The evidence supporting this hypothesis will be reviewed. The need for more sensitive measures to better predict the relative abuse potential of new formulations will be discussed.

## ***Prescription Drugs and the Risks of Abuse, Addiction, and Overdose: Regulatory Challenges***

*Presenter: Deborah Leiderman, M.D., M.A.*

*Director, Controlled Substance Staff Office of the Centre Director,  
CDER; FDA Food and Drug Administration*

## ***Influence of Formulation on the Development of Medications with Abuse Potential***

*Presenter: Robert S. Mansbach, Ph.D.*

Robert S. Mansbach, Ph.D.

Departments of Program Management and Regulatory Affairs, Neurocrine Biosciences Inc.,

The increasing availability of sophisticated drug formulations and delivery devices has created new opportunities in drug development. These newer approaches can result in improved drug bioavailability, or they can alter key pharmacokinetic parameters in such a way as to decrease dosing interval, decrease variability or blunt maximal concentrations that are associated with adverse events of particular concern. Special formulations or devices can also provide for easier or more convenient dosing in subpopulations of interest, such as children or the elderly. Although the key principles of abuse potential assessment and the underlying neurochemistry and pharmacology are relatively well understood, evaluation of the influences of drug formulation have received much less study. Because dose and formulation, and even the therapeutic indication, are refined over the course of development, it is usually difficult to conduct more than a cursory evaluation of the influence of formulation on the underlying abuse potential of the active pharmaceutical ingredient. Industrial sponsors would benefit from further research in several areas: 1) the importance of particular aspects of the pharmacokinetic profile on abuse potential, such as  $T_{max}$ ,  $C_{max}$ , half-life, AUC and Mean Residence Time; 2) the relationship between dosage strength and intoxication or dependence; 3) pharmacokinetic consequences of product tampering; and 4) new methodologies to study formulation-specific abuse, both in the laboratory and in more naturalistic settings. With the increasing regulatory emphasis on prospective risk assessment and minimization, such methods will be important in protecting the public interest while simultaneously providing medications to all who need them.

## ***Abuse Resistant Formulations and the Controlled Substances Act***

*Presenter: Frank L. Sapienza, M.S.*

Frank L. Sapienza, M.S.

The Drug and Chemical Advisory Group, LLC, Fairfax, Virginia

The Controlled Substances Act (CSA) has minimized the diversion of controlled substances at the manufacturing and distribution levels. Recent increased diversion has occurred at the retail level. Levels of diversion and abuse of controlled substances with similar abuse potential and therapeutic indications often parallel availability for medical use, while rates of diversion and abuse may be influenced by factors related to specific products, including their formulations and risk management plans. Abuse deterrent formulations may reduce abuse and attendant adverse health consequences even if the products are diverted. Their development should consider how, to what extent and by whom products containing the targeted substance are abused. It should take into consideration all potential types of abuse including “as is”, multiple doses, alternate routes of administration, physical or chemical separation of the active ingredient, compromised extended release mechanisms and abuse in combination with other substances. Incentives include enhanced corporate image and potentially less restrictive risk management plans or scheduling. Scheduling is substance specific, but the CSA includes products/formulations that are differentially scheduled. These include combination products with narcotic analgesics, single entity products (THC and GHB formulations), barbiturate suppositories and exempt prescription stimulant and depressant drug products. Issues to be considered for differential scheduling under the CSA include 1) whether there is legal authority to do so; 2) application of standard scheduling criteria to individual products; 3) product specific data for “eight factor analyses”; 4) development of predictive data and standards accepted by the scientific and regulatory communities; 5) use of predictive data or post marketing surveillance data; and 6) international treaty obligations. These issues must be addressed before differential scheduling can be considered an incentive for the development of abuse resistant products.

## ***Ephemeral Profiles of Prescription Drug Tampering: Evolving Pseudoscience on the Internet***

*Presenter: Edward J. Cone, Ph.D.*

Edward J. Cone, Ph.D.

ConeChem Research, LLC, Severna Park, MD

The magnitude of non-therapeutic use, or misuse, of prescription pharmaceuticals now rivals that of illicit drug abuse. Drug tampering enables misusers to administer higher doses by intended and non-intended routes. Perceived users’ motives appear to be a combination of interests in achieving a faster onset and enhanced psychoactive effects. Narcotic analgesics, stimulants, and depressants are widely sought, examined and tampered with. The Internet provides broad and varied guidance on tampering methods that are specific to drug classes and unique formulations. Instructions are available on crushing, separation, purification

and chemical alteration of specific formulations to allow changes in dosage, route of administration and time course of effects. Many pharmaceutical formulations contain features that serve as “barriers” to tampering. The nature and effectiveness of formulation barriers vary widely, with some being overcome by adventurous misusers. Examples of successes and failures in tampering attempts are frequently described on Internet sites that support recreational drug use. Successful tampering methods that have widespread appeal evolve into recipes and become archived on multiple websites. Examples of tampering methods include: 1) how to separate narcotic drugs (codeine, hydrocodone, oxycodone) from excipients and non-desirable actives (aspirin, acetaminophen, ibuprofen); 2) overcoming time-release formulations (beads, layers, matrices); 3) removal/release of active drug from high-dose formulations (patches, pills); and 4) conversion of dosage forms for alternate routes of administration. It is recommended that formulators be aware of the extent and ingenuity of tampering practices and formulation barriers that effectively reduce misuse of pharmaceuticals.

***Pre-Meeting Survey of the Views Held by the Conference Participants Regarding the Impact of Formulation & Pharmacometric Technology, Clinical Trial Methodology, and Risk Assessment Knowledge on Abuse Liability, Safety and Regulatory Decisions***

*Presenter: Charles Grudzinskas, Ph.D.*

Charles Grudzinskas, Ph.D.

NDA Partners LLC, and Center for Drug Development Science, UCSF-Washington (DC) Center

Each participant in this CPDD conference on the “Impact of Formulation & Pharmacometric Technology, Clinical Trial Methodology, and Risk Assessment Knowledge on Abuse Liability, Safety and Regulatory Decisions” was required as part of the registration process to provide their viewpoints on a series of questions focused on the specific topics identified below with regard to their impact on “Abuse Liability, Safety and Regulatory Decisions.”

The questions for the survey were proposed and peer reviewed by conference presenters (those confirmed as of January 15, 2005).

Three of the four areas of the survey questions were focused on the role and impact of the following on regulatory decision-making:

- Formulation & Pharmacometric Technology
- Clinical Trial Methodology
- Risk Assessment Knowledge on Abuse Liability Potential.

The fourth area of focus was on the current role of scientific knowledge in influencing regulatory decision-making.

The results of this pre-conference survey will be presented, followed by an open discussion.

## ***Surrogate Manipulations of Drug Kinetics and How They Affect the Abuse Potential of Drugs Using Non-Human Primates***

*Presenter: Robert L. Balster, Ph.D.*

Patrick M. Beardsley, Ph.D., and Robert L. Balster, Ph.D.

Department of Pharmacology & Toxicology and Institute for Drug and Alcohol Studies, Virginia Commonwealth University, Richmond, Virginia

For nearly three decades, our laboratories have been involved with the abuse potential assessment of new chemical entities using physical dependence, drug discrimination, self-administration and other preclinical procedures using mice, rats and rhesus monkeys. We have evaluated representatives from most major classes of CNS therapeutics including opiates, stimulants, depressants, cannabinoids and glutamate antagonists and our data have been used to make regulatory decisions. In our basic science studies, we have observed that surrogates of retarding the onset of action of stimulants can diminish their reinforcing (i.e., abuse-related) effects. For instance, increasing the minimum interval of time between response-produced infusions of cocaine either by distributing their availability in time or by delaying their delivery following completion of responding diminishes their ability to maintain drug-seeking behavior. The effects of these time-dependent decrements on the abuse potential of the stimulants appear dose-dependent with higher doses blunting the magnitude of these reductions in apparent abuse-potential. We will review previously published data how dose and delay of effect can affect drug-seeking behavior in non-human primates. We will also show how our procedures using non-human primates have sorted drugs according to their relative reinforcing effects and how this arrangement compares to their actual assigned schedule within the CSA. We conclude by suggesting how abuse potential studies in animals might be designed to assess the role of variables relating to formulation. (Research in part supported by DA-01442).

## ***Benchtop Testing of Opioid Formulations for Tamper Liability***

*Presenter: Philip A. Goliber, Ph.D.*

Philip A. Goliber, Ph.D., and Curtis Wright IV, M.D., M.P.H.

Purdue Pharma L.P.

Tamper liability is the tendency of a specific formulation to release drug substance in an uncontrolled or inappropriate fashion upon intentional or accidental tampering. It is a physio-chemical characteristic of any formulation, but is a critical characteristic of a controlled substance with significant abuse liability. Since benchtop tamper testing may either direct subsequent human testing or establish that such testing is not essential, it is important that such testing be valid, relevant, comprehensive, reproducible and evaluable. The authors describe, with examples, established methods for benchtop testing of new drug formulations simulating multiple methods of tampering (grinding, chewing, nasal insufflation, “cooking” or preparation for illicit injection) as well as screening for amateur or “kitchen” extractions. A simple classification scheme for reporting tamper liability and tamper resistance is presented along with suggestions for addressing the problem of the predictive power of benchtop testing. (Supported by Purdue Pharma L.P.)

## ***A Novel Technology for Dispensing and Monitoring of Controlled Substances in Research and Therapeutics***

*Presenter: Geoffrey W. Guy, M.D.*

Geoffrey W. Guy, M.D.  
GW Pharmaceuticals

The administration and monitoring of controlled drugs remains problematic in both research and clinical settings. Has the subject or patient taken the medicine as prescribed? Will compliance issues affect the treatment or research results? Heretofore, the answers have been conjectural. Currently, however, RFID, GSM, and fingerprint minutae technologies can be combined to eliminate these variables. Such an advanced dispensing technology contained within hand-held computerized encrypted devices may enhance patient monitoring and compliance by with the following features:

- tracks and records daily patterns and fluctuations in doses in real time
- ensures only authorized providers can dispense, and only authorized patients can access, the medication
- allows remote, real-time computer monitoring and/or modification of dosage by researchers or clinicians
- renders the device secure, tamper-proof, and patient-specific through individualized codes or fingerprint access
- allows delivery of a variety of drug dosage forms, whether tablet, capsule, liquid, injectable, or aerosol
- is suitable for usage with controlled drugs
- disables expired or recalled medications
- reminds patients of time dosing is due
- alerts clinician or third party of patient's failure to take dose.

Various iterations of this technology will be described and discussed.

All work with animals and humans complies with World Medical Association of Helsinki. (Supported by GW Pharmaceuticals.)

## ***Relative Abuse Liability of Opioid Dosage Forms in Canada: Assessing the Potential for Tampering***

*Presenter: Marjie Hard, Ph.D.*

<sup>1</sup>Marjie Hard, Ph.D., <sup>1</sup>Reinhard Schuller, M.S.c., <sup>2</sup>G. L. A. Horbay, Ph.D., and <sup>1,3</sup>Edward M. Sellers, M.D., Ph.D., <sup>1</sup>Ventana Clinical Research Corporation, Toronto, Ontario Canada; <sup>2</sup>Janssen-Ortho Inc., Toronto, Ontario Canada; <sup>3</sup>University of Toronto, Toronto, Ontario Canada

**BACKGROUND:** Fentanyl is attractive to opiate abusers, even if it is in a formulation that is difficult to abuse. The objective of this study was to assess the potential for tampering with a fentanyl matrix patch (FM) compared to other opioid formulation types in Canada.

**METHODS:** Recreational opioid users experienced in prescription opioid tampering (n=42) from 3 Canadian cities were presented with 9 products (some hypothetical), i.e. 3 different formulations, [tablet (T), reservoir gel patch (G) and matrix patch (M)] for each of 3 opioid drugs, [fentanyl (F), oxycodone (O) and hydromorphone (H)]. Abuse potential was assessed using 7-point Likert scales (Value of Product, Likelihood to Tamper), rank order of overall desirability and a validated Opiate Attractiveness Scale (Butler, in prep.). Comparisons of each formulation to the FM were made on rank data using nonparametric methods.

**RESULTS:** FT, FM and HT were highly valued and most likely to be tampered with. The decreasing order of desirability was FT>HT>FM>FG>OT>HM>HG>OM>OG. OT ranked as the most attractive on the Opiate Attractiveness Scale. FM was significantly more attractive than all the gel products (FG, HG, OG: P<0.001) and was statistically similar in attractiveness to FT, HT, OT and OM.

**CONCLUSIONS:** These data suggest that a FM formulation has characteristics that indicate a risk of diversion and tampering. This should be confirmed by prospective epidemiological studies. Comparative risk evaluation among formulations should be part of the development of any new delivery system. (Supported by Janssen-Ortho Inc.)

## ***A New Technology to Increase the Mechanical Stability of Matrix Tablets to Prevent Abuse by Crushing or Chewing***

*Presenter: Judy Ashworth, M.D.*

J. Bartholomaeus, Elizabeth Arkenau, Ph.D., Judy B. Ashworth, M.D.  
Grunenthal GmbH

**Background:** Many currently marketed, controlled-release formulations of opioid analgesics can easily be tampered with, compromising the intended slow release of the active ingredient. To allow for intravenous or intranasal abuse, they are first crushed into a powder. Orally, they may simply be chewed to allow for rapid release of the entire dose. In response, we have developed a new technology to produce controlled-

release tablets with enhanced mechanical stability that makes it nearly impossible to crush or chew. To test the mechanical stability, a test battery was developed and performed. Methods: A test battery to challenge the mechanical stability of this new abuse deterrent formulation was performed including cutting, grinding, pounding and crushing under various conditions. Additional tests were conducted to attempt to dissolve the tablet in various solutions including water, alcohol, oil, soap, acids and bases. Results: The test tablets could not be crushed and/or ground in a powder. In the dissolution tests, under all conditions, the tablets slowly dissolved, forming a viscous gel. Conclusions: This new abuse deterrent formulation should help deter the abuse and diversion of controlled-release opioids by making them much less attractive to the drug dealer and the abuser.

### ***The Development of Opioid Formulations with Limited Diversion and Abuse Potential***

*Presenter: Paul J. Fudala, Ph.D., R.Ph.*

Paul J. Fudala, Ph.D., R.Ph.

VA Medical Center, Philadelphia and University of Pennsylvania School of Medicine

The nonmedical use of prescription opioid medications is not a new phenomenon, but such use has been increasing in recent years. Various methods have been used and continue to be developed in an effort to limit diversion and abuse of these medications. A number of these methods will be described for opioid analgesic and addiction treatment formulations using relevant historical examples as well as examples of formulations currently under development. The focus will be on those formulations that represent a combination of an opioid agonist with an antagonist. Consideration will be given to the pharmacokinetic profile of the agonist and antagonist, the expected primary route of abuse of the medication and the medication combination, the dose of medication that is likely to be abused, the availability of alternative drugs of abuse, and the population of abusers which is being targeted with the revised formulation.

### ***Adding Naloxone to Opioids to Decrease Abuse Potential: Rationale, History and Evidence of Efficacy***

*Presenter: Eric C. Strain, M.D.*

Eric C. Strain, M.D.

Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

The addition of naloxone to an opioid analgesic used via a non-parenteral route can decrease the parenteral abuse potential of the opioid. Naloxone has been used in this way for two marketed products (pentazocine and buprenorphine), and investigated for a third (methadone). Pentazocine, an opioid mixed agonist-antagonist that is marketed for analgesia, was parenterally abused in the United States when combined with tripeleminamine (“Ts and Blues”) in the late 1970s. The addition of naloxone to pentazocine essentially halted this problem. Methadone combined with naloxone was extensively tested in human laboratory studies

and clinical trials in the early 1970s, but has had minimal subsequent development (although renewed interest may be prompted by proposals for office based treatment with methadone). Buprenorphine combined with naloxone is a relatively recent innovation that can be viewed, in part, as a U.S. response to abuse of buprenorphine monotherapy tablets in other parts of the world. The purpose of this presentation is to describe the rationale for use of naloxone to decrease abuse liability of medications, to provide a historical overview to the three opioid medications that have been investigated as a combination product with naloxone, and to present data from a human laboratory study that examined the acute effects of the buprenorphine/naloxone combination. While combination products containing naloxone appear to decrease abuse potential, such formulations do not ensure an absence of diversion and abuse. This talk will also address those populations for which an opioid combined with naloxone will not significantly address potential diversion and abuse. (Supported by grants DA00332 and DA08045 from the National Institute on Drug Abuse.)

***Abuse Liability of Intravenous Buprenorphine, the Buprenorphine/Naloxone Combination, and Methadone in Recently Detoxified Heroin Abusers***

*Presenter: Sandra D. Comer, Ph.D.*

Sandra D. Comer, Ph.D., Maria A. Sullivan, M.D., Ph.D., Eric D. Collins, M.D., and Marian W. Fischman, Ph.D.  
Columbia University

Buprenorphine is used worldwide as a safe and effective medication for treating pain and, more recently, for treating substance abuse. Because of its partial mu opioid agonist profile, it was believed that the abuse potential of buprenorphine itself would be low. However, several countries have reported a growing incidence of buprenorphine abuse. The present series of studies was designed to examine the abuse liability of buprenorphine alone, buprenorphine in combination with naloxone, and methadone. Participants were dependent on heroin upon admission to the hospital. During the first one to two weeks after admission, participants were detoxified and then the effects of a range of doses of each study drug were examined. The reinforcing, subjective, performance and physiological effects of each drug were measured both before and repeatedly after drug administration. Buprenorphine was self-administered above placebo levels in all of the studies, indicating that it serves as a reinforcer. The reinforcing effects of buprenorphine were not significantly different from methadone or from the buprenorphine/naloxone combination. The subjective effects of buprenorphine were not different from methadone, but they were greater than the combination. These results demonstrate that in recently detoxified heroin abusers, buprenorphine has moderate to robust reinforcing effects. However, several studies have demonstrated that the pharmacodynamic effects of buprenorphine are reduced to a greater extent than full mu agonists in opioid tolerant individuals. In particular, the effects of the buprenorphine/naloxone combination should have substantially reduced abuse liability because parenteral administration of this medication would precipitate opioid withdrawal in opioid tolerant patients. (Supported by DA10909.)

## ***Phase 1 Testing of Opioid Agonist-Antagonist Formulations in Man***

*Presenter: Stephan C. Harris, M.D.*

Stephan C. Harris, M.D., Vijan Vashi, Ph.D., S. Cipriano, Peter Perrino, M.D.,  
and Donald Cilla, Pharma.D.  
Purdue Pharma L. P.

Conventional abuse liability testing of drug substances is a mature area of research where both methods of study and subject populations appropriate for study are well established. The desire to develop dosage forms that modify the intrinsic desirability of a drug substance for purposes of reducing abuse while maintaining therapeutic effects imposes regulatory, organizational and subject requirements not ordinarily part of such testing. The authors describe the development of methods of evaluation that bridge the gap between academic research laboratory testing and the process of Phase 1 development of a new opioid analgesic formulation, providing examples of Phase 1 designs that examine safety in overdose situations, elucidate pharmacokinetic characteristics of typical tampering techniques, and evaluate effects on analgesic efficacy. The importance of connecting the preclinical characteristics observed in formulation development to clinical trials design features, as well as important lessons on study conduct, subject selection and interpretation of results, will be discussed. It is the opinion of the authors that successful Phase 1 testing of abuse liability related properties requires the integration of conventional pharmaceutical Phase 1 testing methods with the facilities and capabilities of experts in human subjects research into abuse and addiction. (Supported by Purdue Pharma L.P.)

## ***Ultra-low-dose Naltrexone Reduces Addictive Potential of Oxycodone in Rats***

*Presenter: Lindsay H. Burns, Ph.D.*

Francesco Leri, Ph.D.,<sup>1</sup> Mary C. Olmstead Ph.D.,<sup>2</sup> and Lindsay H. Burns Ph.D.,<sup>3</sup>

<sup>1</sup>University of Guelph, Guelph, ON, Canada; <sup>2</sup>Queen's University, Kingston, ON, Canada;

<sup>3</sup>Pain Therapeutics, Inc. South San Francisco, CA, USA

**AIM:** Oxytrex™, a novel drug candidate for severe chronic pain, is a proprietary combination of oxycodone and ultra-low-dose naltrexone, an opioid antagonist. A clinical trial in osteoarthritis showed significantly greater pain relief from oxycodone + ultra-low-dose naltrexone than from oxycodone alone. Ultra-low-dose opioid antagonists also alleviate opioid tolerance and dependence in rodents. Here we assess the abuse potential of oxycodone + ultra-low-dose naltrexone versus oxycodone in rat models of drug reward, drug-taking and drug-seeking.

**RESULTS:** Using the conditioned place preference paradigm, time spent in an environment previously paired with oxycodone + ultra-low-dose naltrexone or with oxycodone indicated the rewarding potency of each. Rats showed a conditioned place preference to oxycodone but not to oxycodone + ultra-low-dose naltrexone, suggesting a lack of rewarding effect from the combination. In self-administration, rats took

more infusions of the combination than of oxycodone alone, suggesting a lower rewarding potency for oxycodone + ultra-low-dose naltrexone. Following self-administration, drug-seeking was elicited by a “free” injection of oxycodone or by foot-shock stress, mimicking triggers of relapse in human addicts. Drug-seeking was significantly reduced in the oxycodone + ultra-low-dose naltrexone group. Finally, rats self-administered oxycodone or oxycodone + ultra-low-dose naltrexone under a schedule of increasing lever-pressing requirements to test motivation for drug-taking. A greater percentage of rats taking oxycodone + ultra-low-dose naltrexone ceased responding, i.e. reached the “break-point,” when response requirements were high.

**CONCLUSIONS:** Previously shown to enhance oxycodone analgesia, ultra-low-dose naltrexone may simultaneously reduce oxycodone’s potential for abuse and addiction. These rat studies suggest that ultra-low-dose naltrexone may suppress the rewarding properties of oxycodone and the vulnerability to relapse, possibly by reducing opioid-induced neuroadaptive changes that contribute to addiction. (Supported by Pain Therapeutics, Inc.)

### ***A Novel, Long-Acting Oxycodone Formulation Deters Abuse in Humans***

*Presenter: Nadava Friedmann, Ph.D., M.D.*

Nadava Friedmann, Ph.D., M.D.<sup>1</sup>, Annelies W. de Kater, Ph.D.<sup>1</sup>, Peter G. Butera<sup>1</sup>, Lynn R. Webster, M.D.<sup>2</sup>, Stewart Ratcliffe, M.D.<sup>3</sup>, Petronella A. van Raders<sup>3</sup>, and Richard M. Langford, M.D.<sup>3</sup>

<sup>1</sup>Pain Therapeutics, Inc., South San Francisco, CA; <sup>2</sup>Lifetree Clinical Research, Salt Lake City, UT; <sup>3</sup>St. Bartholomew’s Hospital, London, U.K.

**AIM:** Abusers of controlled-release (CR) oxycodone crush these tablets to extract the full dose of oxycodone, resulting in an immediate, large spike in oxycodone blood levels, a powerful morphine-like high, and possible respiratory depression or death. In the US, oxycodone abuse resulted in over 20,000 ER visits and hundreds of deaths in 2002. Remoxy™ is an abuse-resistant long-acting oxycodone formulation in clinical development that cannot be abused by heating, freezing, or crushing and dissolving in water, alcohol or other common beverages. This study examines the effects of abusing this novel formulation on subsequent plasma oxycodone levels.

**METHODS:** In healthy male volunteers, the pharmacokinetics of this abuse-resistant long-acting oxycodone vs. the commercially available CR oxycodone are compared after swallowing whole or after crushing and ingesting with water or alcohol. After each dosing, plasma oxycodone levels were monitored for 48 hours and compared to those produced by an immediate-release (IR) oxycodone formulation.

**RESULTS:** The abuse-resistant long-acting oxycodone and the commercial CR formulation produced similar plasma oxycodone levels when each was swallowed whole as intended. After crushing and ingesting with water or alcohol, the commercial CR formulation resulted in even higher oxycodone plasma concentrations than those produced by the IR oxycodone tablet. In contrast, oxycodone plasma concentrations after crushing the abuse-resistant long-acting oxycodone were markedly lower at early time-points compared to both the IR or crushed commercial CR formulations, and only slightly above levels produced by swallowing whole.

CONCLUSIONS: These results demonstrate this novel abuse-resistant long-acting oxycodone to be a safer alternative to commercially available CR oxycodone. The expected benefits include less illicit use, less oxycodone diversion and fewer oxycodone-related fatalities. (Supported by Pain Therapeutics, Inc.)

### ***Methylphenidate Transdermal System (MTS) for the Treatment of ADHD***

*Presenter: Geoffrey Dugue, M.D., M.P.H.*

<sup>1</sup>Geoffrey Dugue, M.D., M.P.H., and <sup>2</sup>Raymond D. Pratt, M.D.

<sup>1</sup>Noven Pharmaceuticals, Inc.; <sup>2</sup>Shire Pharmaceuticals Inc.

ADHD is a neurobehavioral disorder occurring in 5% to 10% of school age children. The disorder persists into late adolescence and adulthood in up to 60% of cases and current estimates are that 3% to 4% of adults have ADHD. Stimulant medications (methylphenidate and amphetamine compounds) are highly effective in ameliorating the symptoms of ADHD in all age groups and continue to be the mainstay of treatment for this disorder. Concerns, however, have been raised regarding the potential for diversion of prescribed oral stimulants for non-medical use. A novel methylphenidate transdermal system (MTS) recently has been developed for the treatment of ADHD. The MTS patch consists of a multi-polymeric adhesive matrix that serves to both hold the drug and adhere to the skin. The matrix MTS system is designed to provide a steady delivery of d,l-methylphenidate during the dosing interval (patch wear time). This alternative delivery system has several potential advantages over oral therapy, including flexibility to adjust the daily duration of effect, as well as increased convenience and compliance. The MTS matrix technology and extended-release nature of the product would appear to limit the potential for abuse, in part, by eliminating the most preferred method of MPH abuse - that of crushing oral tablets and snorting or injecting the resulting powder.

### ***Novel 6-Month Buprenorphine Dosage Form for Treatment of Opioid Dependence***

*Presenter: Lauren C. Constantini, Ph.D.*

<sup>1</sup>Lauren C. Costantini, Ph.D., <sup>2</sup>Jason White, Ph.D.,

<sup>3</sup>James Bell, M.D. , <sup>4</sup>John Saunders, M.D., <sup>1</sup>Dimitri Lissin, M.D.

<sup>1</sup>Alan Jacobs, M.D., <sup>1</sup>Sofie Kleppner, Ph.D., and <sup>1</sup>Raj Patel, Ph.D.

<sup>1</sup>Titan Pharmaceuticals, Inc., South San Francisco, CA, USA; <sup>2</sup>University of Adelaide, Adelaide, Australia;

<sup>3</sup>The Langton Center, Sydney, Australia; <sup>4</sup>University of Queensland and the Royal Brisbane and Women's Hospital and Prince Charles Hospital Districts, Brisbane, Australia

The safe and efficacious use of sublingual (SL) buprenorphine for the treatment of opioid dependence is well established. However, in addition to restricted and supervised dosing requirements and variable blood levels that occur after SL dosing, the potential for abuse and diversion is potentially a significant problem, with reports of patients crushing and injecting tablets. These limitations may restrict the potential and utilization of this effective medication. Probuphine is a novel subcutaneous implant dosage form of buprenorphine for the treatment of opioid dependence. The implant is inserted subcutaneously into a site

such as the inner upper arm, and achieves sustained and stable plasma buprenorphine concentrations over 6 months. Each implant is comprised of a solid matrix of buprenorphine and ethylene vinyl acetate, and measures 26 mm in length by 2.4 mm in diameter. The capacity to provide opioid-dependent patients with a continuous source of an effective treatment will potentially improve the issues noted above, including importantly the potential for abuse and diversion. The physician directly administers the buprenorphine implant to the patient in the office/clinic, significantly reducing the ability of the patient to easily abuse or divert their medication. An open-label, two-dose-group, 6-month clinical study of this buprenorphine implant confirmed the safety and identified the therapeutic dose relationship between implants and SL buprenorphine. Patients were switched from maintenance SL buprenorphine to buprenorphine implants. Results showed stable buprenorphine plasma levels, control of withdrawal symptoms and heroin cravings, and no significant side effects over the 6 month study. Probuphine has the potential for significant advantages over SL buprenorphine for maintenance treatment of opioid dependence. (Supported by Titan Pharmaceuticals, Inc.)

### ***The Impact of Abuse Deterrent Formulation on the Incidence of Abuse and Diversion of OROS® Methylphenidate***

*Presenter: Robert L. DuPont, M.D.*

<sup>1</sup>Robert L. DuPont, M.D., and <sup>2</sup>Stephen D. Lande, Ph.D.

<sup>1</sup>Bensinger, DuPont and Associates; <sup>2</sup>Interactive Forums, Inc.

Stimulants are the most widely used drugs in the treatment of attention deficit hyperactivity disorder (ADHD), and methylphenidate (MPH) is the most commonly prescribed stimulant for the treatment of ADHD. MPH is chemically related to the amphetamines, which have an established history of drug abuse, and because MPH itself has abuse potential, it has been classified as a controlled substance.

OROS® methylphenidate is a sustained-release, once-a-day MPH formulation for the treatment of ADHD that has physical properties, which may deter abuse and diversion for non-medical use. Each OROS® methylphenidate system consists of an inner core that provides slow release of MPH over a period of 10 hours, surrounded by a rigid, semipermeable membrane with an immediate release drug outercoat. The OROS® tablet is difficult to crush and the result of crushing is an irregular mixture of large and small pieces that resists intranasal and intravenous administration. OROS® methylphenidate deters abuse because of the slow rate of MPH release from an intact system and the considerable effort required to extract and reformulate its components into an abusable form of MPH.

This presentation will review the findings of a comprehensive risk monitoring program designed to evaluate actual and potential abuse and diversion of OROS® methylphenidate including:

- Abuse liability studies conducted to evaluate the potential for abuse and ease of diversion of OROS® methylphenidate;

- Analyses of existing databases providing information about the frequency of abuse and diversion of MPH products;
- Surveys about MPH abuse among various demographic groups, including vulnerable populations such as adolescents, young adults and drug abusers; and
- Surveys of public literature on the topics of abuse and diversion of stimulants in general and MPH in particular.

### ***The Question of Tolerance: Cannabis Based Medicine Provides Long-Term Clinical Efficacy without Dosage Increases or Withdrawal***

*Presenter: Geoffrey W. Guy, M.D.*

Geoffrey W. Guy, M.D.  
GW Pharmaceuticals

Many psychoactive drugs induce tolerance: a temporal loss of pharmacological effects. This presentation will review historical and new data from long-term safety studies (SAFEX) of patients employing Sativex®, a 1:1 tetrahydrocannabinol (THC): cannabidiol (CBD) cannabis based medicine (CBM) administered oro-mucosally, and now an approved pharmaceutical in Canada.

Cannabinoid tolerance is mainly pharmacodynamic in nature with changes of cannabinoid receptor density in the brain. In humans, marked tolerance is observed to cannabis side effects in chronic administration: tachycardia, hypothermia, orthostatic hypotension, dry mouth, and ocular injection, while tolerance to subjective effects is noted with high dose oral THC.

The use of CBM oro-mucosally for MS symptoms of pain, spasticity and sleep disturbance, peripheral neuropathic pain, bladder dysfunction, rheumatoid arthritis and intractable cancer pain in clinical trials and SAFEX studies employing CBM, with over 800 patient-years of exposure, is reported. Data will demonstrate low-nil subjective patient intoxication scores, with progressively diminished adverse event profiles over time of usage, and consistent maintenance of symptom control with stable or even diminishing dosage. CBM in chronic administration demonstrates tachyphylaxis to side effects, with no tolerance developing to its clinical benefits, and little evidence of withdrawal upon temporary experimental discontinuation.

All work with animals and humans complies with World Medical Association of Helsinki. (Supported by GW Pharmaceuticals.)

Day 2: April 20, 2005

***Exempt Preparations: Historical Perspectives***

*Presenter: Louis S. Harris, Ph.D.*

Louis S. Harris, Ph.D.

Medical College of Virginia-VCU Dept of Pharmacology & Toxicology

The first serious consideration of “exempt” preparations” probably occurred during the deliberations of the League of Nations during a 1931 Convention. Thus, a section on “Exempt Preparations” was written into the 1931 “Convention for Limiting the Manufacture and Regulating the Distribution of Narcotic Drugs” (1931 Convention). After the Second World War, the United Nations (UN) felt it incumbent to revise the 1931 Convention in light of the then present situation and convened another “convention” which resulted in the “Single Convention on Narcotic Drugs, 1961,” which was amended by a 1972 Protocol Amendment (Single Convention). It later became apparent that the Single Convention could not accommodate the marked increase in new psychotherapeutic agents and psychotropic drugs which also had great potential for abuse. Accordingly, another Convention was initiated which resulted in the “Convention on Psychotropic Substances 1971” (1971 Convention).

Following the lead of the 1931 Convention, the 1961 Convention defined preparations as “a mixture, solid or liquid, containing a drug.” Drugs in Schedule I and II could be exempted from certain control measures if they were compounded with one or more ingredients and in low concentrations and/or which would prevent ready extraction of the active drug by readily applicable means or in a yield which would constitute a risk to public health. Later, preparations which contained ingredients which would strongly discourage misuse were added. The 1971 Convention introduced a much larger array of substances which were prescribed as mixtures. Thus, special provisions were included (Article 3) regarding control of preparations. However, the definitions were quite similar and carried over to the United States Controlled Substances Act (CSA). Historically, decisions about exempt preparations required little scientific basis. For instance, diphenoxylate, an anti-diahrreal agent, was exempted by the addition of a small amount of atropine (Lomotil). This was first suggested at a hearing of the Committee on Drug Addiction and Narcotics (the predecessor of the current College on Problems of Drug Dependence) called at the request of a pharmaceutical firm. Other examples will be discussed. However, it should be pointed out that “exempt preparations” are only exempted from certain provisions of the conventions and CSA and the active substance is still controlled under the appropriate schedule.

## ***Research Design Strategies to Evaluate the Impact of Formulation on Abuse Liability***

*Presenter: Edward M. Sellers, M.D., Ph.D.*

Edward M. Sellers, M.D., Ph.D., Shelley McColl, Ph.D., and Howard L. Kaplan, Ph.D.  
Ventana Clinical Research Corporation and University of Toronto, Toronto, Canada

Scheduling of an active chemical drug substance under the Controlled Substances Act (CSA) is established by evaluation of preclinical, clinical safety, and experimental abuse liability studies, as well as information on diversion and overdose. Formulations that mitigate abuse liability, dependence potential and public health risks (e.g., altered absorption rate and tamperability; long half-life; pro-drugs; combination products) are amenable to preclinical and clinical studies to compare their abuse potential to reference compounds. For new formulations (NF) as marketed agents, direct comparison to the immediate release (IR) formulation of the reference compound is typically needed across the full range of potential studies.

While the public health advantage of formulation changes in the marketplace can be conceptualized in behavioural economic terms, generating persuasive data is challenging. Study complexity increases because of additional conditions (e.g., placebo, IR 2-3 doses, NF 2-3 doses, unscheduled or negative control 2-3 doses), larger sample sizes (study power driven by the comparison of NF vs IR or placebo), and associated increases in study duration. However, the number of study arms can be reduced by using single maximal doses of well-characterized controls, and study duration can be reduced by using incomplete block designs. Less typical experimental approaches may also be useful such as human choice or discrimination procedures or pre-marketing consumer studies among experienced drug tamperers.

New formulations that demonstrate a substantial difference from marketed or reference products have a potential marketing advantage and require a less onerous risk management. Post-marketing epidemiologic data demonstrating the lack of abuse will be most persuasive from a public health and physician perspective.

## ***Regulatory Challenges for New Formulations in Today's Environment***

*Presenter: Cynthia G. McCormick, M.D.*  
*McCormick Consultation, LLC*

## ***Risk Identification, Risk Assessment, and Risk Management of Abusable Drug Formulations***

*Presenter: Curtis Wright, IV, M.D., M.P.H.*

Curtis Wright, IV, M.D., M.P.H., E. Douglas Kramer, M.D., and Mary-Ann Zalman, Ph.D.  
Purdue Pharma L.P.

The evaluation of pharmaceuticals for abuse potential and attempts to manage those risks through development of new pharmaceuticals and dosage forms is both a new topic and a very old topic in pharmaceutical science. Intentional abuse has been identified as the societal concern limiting use of opioids and alcohol for millennia and for stimulants and GABA-ergic sedative-hypnotics for almost a century. Despite this societal need to control abuse, attempts to develop pharmaceutical opioids and tranquilizers that are less liable to abuse have met with only limited success and have resulted in rejection of such efforts as futile by some research organizations, limiting resources and opportunities for development. If such products are to be developed, clear and defensible standards for pre-approval abuse liability testing are necessary. The increases in the magnitude of prescription drug abuse in the United States in the past few years have increased the risk of abuse of all medications with abuse potential. The result has been that if new products are to be promoted as presenting less risk of abuse, there must be proof of such claims, demonstrated by a systematic post-marketing study conducted in a manner that will allow scientifically and epidemiologically valid conclusions to be reached concerning abuse liability relevant to existing products in the same indication. If pharmaceuticals with lower potential for abuse are to be effectively utilized by the healthcare system, the validity of specific post-marketing measures of comparative abuse liability must have broad medical and scientific acceptance. (Supported by Purdue Pharma L.P.)

## ***Risk Management Action Plans for Opioids Now and in the Future***

*Presenter: Edgar H. Adams, Sc.D.*

Edgar H. Adams, Sc.D.  
Consultant

Over the last 10 years, the FDA has increased its emphasis on Risk Management and Post Marketing Surveillance. In 1992, an extensive post-marketing program was developed to support the approval of tramadol as a non-scheduled analgesic under the Controlled Substances Act. In contrast, subsequent approvals of opioids scheduled under the CSA, including extended release oxycodone and extended release morphine, did not include risk management programs other than the standard reference for compliance with 21 CFR 314.80 and 314.81. At the turn of the century, dramatic increases in the prevalence of the nonmedical use of analgesics as measured by the National Household Survey of Drug Abuse and

consequences associated with the abuse of analgesics exhibited in the Drug Abuse Warning Network (DAWN) were noted. For example DAWN mentions of oxycodone increased from approximately 6,000 in 1999 to more than 22,000 in 2002. These increases coupled with extensive media coverage of OxyContin® fueled concerns about the abuse of opioids spreading to relatively naive populations. As a result, the recent approval letters for Subutex-Suboxone® (C-III) and Palladone (C-II) include extensive requirements aimed at monitoring the diversion of these products to populations for whom the drug is not intended. However, the recent approval of generic extended release oxycodone does not contain these requirements. This paper will review the recent history of these efforts, their adequacy, the lack of parallel requirements for generics and the increased use of these programs in the future.

### ***Research Issues and Experiences in Studying Prescription Drug Diversion***

*Presenter: James A. Inciardi, Ph.D.*

James A. Inciardi, Ph.D., and Hillary L. Surratt, Ph.D.

University of Delaware Research Center

Prescription drug diversion, the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace, occurs primarily through: 1) the illegal sale of prescriptions by physicians and pharmacists; 2) “doctor shopping” by individuals who visit multiple physicians to obtain prescriptions; 3) theft, forgery, or alteration of prescriptions by patients; 4) robberies and thefts from pharmacies; 5) thefts of institutional drug supplies; 6) burglaries; and 7) Internet sales. Although diversion is estimated to be a \$25 billion-a-year industry, only minimal empirical data are available on the nature and extent of diversion. Problems facing the systematic study of diversion include locating police and regulatory agencies that investigate diversion, eliciting their agreement to participate in research studies, overcoming differences in what kinds of data researchers need and what police agencies typically collect, establishing denominators and estimating rate, and obtaining data on a consistent basis. In a diversion study conducted by the University of Delaware and funded by Purdue Pharma, many of these issues and problems were resolved, and will be discussed. During the period January 2002 through mid-2004, 250-300 diversion investigators in all 50 states were surveyed on a quarterly basis. In the jurisdictions targeted, there were a total of 29,025 diversion cases investigated during the 10-quarter survey period. Of these cases, 37.5% involved hydrocodone, followed by oxycodone (24%), morphine (4%), methadone (2.9%), hydromorphone (2.1%), and fentanyl (1.9%), and a variety of other drugs. Data will be presented on approaches for illustrating trends in diversion. (Supported by Purdue Pharma, L.P.)

## ***Measuring Rates of Nonmedical Use - Dimensions and Denominators***

*Presenter: Meredith Y. Smith, Ph.D.*

Meredith Y. Smith, Ph.D., and J. David Haddox, D.D.S., M.D.  
Purdue Pharma L.P.

**BACKGROUND:** Surveillance for nonmedical use and diversion is an essential component of a risk management program for drugs with abuse potential, such as prescription opioids. Major challenges include identifying and integrating disparate data sources at the community level, and analyzing these data spatially, temporally and by an appropriate denominator. Methods are needed to estimate the number of individuals at risk for abuse within discrete geographic areas that adjust for differences in the relative market availability of different drug compounds over time.

**METHODS:** The authors provide an overview of a comprehensive, multi-dimensional framework for prescription opioid surveillance. Different sources of numerator data will be discussed, as well as issues associated with the selection and application of denominator data for rate calculation purposes and methods for modeling geographic and temporal trends.

**RESULTS:** Key sources of numerator data include drug safety and pharmacovigilance reports, community-based law enforcement reports regarding local abuse and diversion activities; drug abuse treatment facility admissions data; and intentional exposure calls to poison control centers. Sources of denominator data include: census data, number of opioid prescriptions dispensed, kilograms of drug distributed, and number of patients receiving opioid prescriptions. Alternative denominators yield different rankings in terms of the degree of nonmedical use and diversion, and alter the risk-benefit ratio for different products. Temporal analyses using Poisson regression show incidence patterns independent of denominator type.

**CONCLUSION:** An effective risk management program for prescription opioids requires a multi-dimensional perspective that permits local capture of information and monitoring of trends both temporally and spatially. (Supported by Purdue Pharma L.P.)

## ***The Standards for Risk Management Plans for High Abuse Potential Medications***

*Presenter: J. David Haddox, D.D.S., M.D.*

J. David Haddox, D.D.S., M.D., and Sidney H. Schnoll, M.D., Ph.D.  
Purdue Pharma L.P.

High-dose, modified-release dosage forms of Schedule II drugs are currently considered by certain regulatory authorities to have the highest risk of adverse outcomes associated with abuse of the available licit drugs. Regulatory approval for marketing of these medications may require negotiation of an acceptable Risk Management Program intended to help prevent, detect and deter injury to the public associated with abuse or misuse of the product. The authors describe the essential components of the risk management plan for a recently approved modified-release, oral hydromorphone; discussing labeling, patient education materials, professional and public educational requirements, surveillance, reporting, launch controls, and interventions. The authors describe how this program establishes the current de-facto standard for modified-release opioid formulations. They also describe how such plans should be modified for newer products with specific formulation modifications demonstrated to be effective in reducing either the risk of abuse or the health consequences of such abuse. The authors discuss the limitations of such plans in addressing the societal problem of prescription drug abuse and offer suggestions as to how the information developed can be made useful to social agencies tasked with dealing with the problem. (Supported by Purdue Pharma L.P.)

## ***Risk Management Solutions for New Drug Formulations: Path to More Flexible CSA Scheduling Options?***

*Presenter: Jack E. Henningfield, Ph.D.*  
*Pain Therapeutics, Inc.*

Jack E. Henningfield, Ph.D., Edward J. Cone, Ph.D., R.V. Fant, K.L. Sees, and J.M. Pinney  
Pinney Associates Inc., Bethesda, Maryland

New drug formulations are developed to provide therapeutic advantages such as longer action or more convenient routes of administration (e.g., transdermal and inhalation). When controlled substances are involved, concerns may arise about their attractiveness for abuse and diversion. These concerns may be addressed in part by the formulation of the drug, but there are limitations on the degree to which physical characteristics can reduce abuse and diversion. A risk management program may be crucial for approval, by providing a basis for reducing and detecting unintended consequences while laying the foundation for future considerations such as down scheduling or expanded indications.

Ideally, basic elements of risk management are developed early in drug development. Unanticipated circumstances (e.g., drug misuse may attract media coverage that fuels additional misuse, abuse and diversion) may further dictate the need for testing of other drugs in the same category to estimate their risk of abuse and diversion (e.g., methods of tampering and administration, attractiveness to substance abusers and illicit distributors). Incorporation of effective risk management considerations early in development may also be a consideration in scheduling decisions and the constraints on marketing. In all cases, comprehensive risk management programs that help reduce and detect potential abuse and diversion can ensure patient access and maximize therapeutic benefits.

