2nd Human Abuse Liability & Abuse-Deterrent Formulations

Avoid Regulatory Penalties and Improve Market Success by Clearly Demonstrating Reduction of the Abuse Potential in New and Existing Drugs

November 2-3, 2015 | Hyatt Regency Bethesda | Bethesda, Maryland

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PFIZER

Joseph Stauffer
CMO
CARA THERAPEUTICS

Preclinical and Clinical Techniques to Minimize Drug Abuse Potential

Regulatory and Methodological Updates for Demonstrating Abuse Potential!

- **AMNEAL** Analyzes Patents for Generic Oxycodone Formulations
- **PFIZER** Improves the Clinical Predictive Value of Preclinical Abuse Potential Models
- **ATLANTIC PHARMA** Pursues Generic Candidates After Changes to Regulatory Tiered Safety Claims

Technical Breakthroughs in Abuse-Deterrent Formulations!

- **CARA THERAPEUTICS** Refines Non-Addictive Kappa Opioids
- **RECKITT BENCKISER** Designs Subcutaneous Time-Release Opioids to Eliminate Oral Supply
- **ACURA PHARMA** Prepares for Anti-ADF Countermeasures from Drug Abusers

Improvements in Abuse Liability Trial Design!

- **MITSUBISHI TANABE PHARMA** Ranks the Best Pain Scales for Trial Questionnaires
- **TEVA** Coordinates Abuse Data Monitoring Strategies
- **UPSHER-SMITH** Accounts for Missing Data in Statistical Analysis

“Helpful, thought-provoking, and very interesting presentations. I appreciated the rich source of data and information.”
—Manager, Regulatory Affairs, SUNOVION

“Excellent presentations and good dialogue.”
—Senior Director, Clinical Research, EGALET CORPORATION

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Dear Colleague,

Popular concern over the addiction potential of opioid analgesics, as well as stimulants, benzos and other drugs, is putting tremendous pressure on the drug industry. Amidst fears from patients, physicians and payers, the past year has seen the FDA release several different versions of regulatory guidelines clarifying their expectations for both the technical development of less addictive drugs as well as for best practices in designing preclinical and clinical studies that give the most accurate assessment of a drug’s abuse potential.

Now in its second year, ExL Events’ Human Abuse Liability & Abuse-Deterrent Formulations conference is the only event available that gives you in-depth industry knowledge on the approach required for demonstrating the improved safety of your opioids and other potentially addictive therapeutics in order to improve market potential. Join us this year to learn how to:

✧ Adapt to new and pending regulatory guidelines for both branded and generic drugs
✧ Design analgesics that have a non-addictive pharmacology
✧ Select the most appropriate comparator drugs and adverse event terminology during clinical research
✧ Minimize the abuse risk of drugs through multiple delivery mechanisms, including oral, topical and subcutaneous
✧ Employ the ideal data tracking techniques to illustrate changes in the real abuse levels of specific drugs and formulations
✧ Engage with more than 100 industry experts on the latest regulatory and technical approaches for lowering the abuse potential of prescription drugs

We look forward to welcoming you to Bethesda this fall!

VENUE INFORMATION:
Hyatt Regency Bethesda
One Bethesda Metro Center
Bethesda, MD 20814

WHO SHOULD ATTEND:
Pharmaceutical, biotechnology, and medical device professionals responsible for:
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This Program May Also Be of Interest to:
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- HAL Service Providers
✧ CMOs
✧ REMS/Pharmacovigilance Specialists
✧ Drug Abuse Registry/ Surveillance Specialists

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9:00  Chart a Path Forward for Generics that Lack the Tiered Information of Branded Products

The 2015 FDA guidance on abuse-deterrent formulations differs from prior versions in that it eliminates the separate tiered structures of scientific and regulatory credibility lent by pairing specific types of tests. As the industry awaits the guidelines for abuse-detergent generic drugs later this year, what is the most reliable way to advance our understanding across different product categories that had previously ranked safety information according to now-unnecessary tiers?

• Predict the conflicts that may arise in developing generics for branded drugs with specific tiered safety claims
• Build a better understanding of the likely regulatory outcomes
• Determine whether your archival tiered safety data can still be put to scientific or marketing use

Kevin Sills, Vice President, R&D, ATLANTIC PHARMACEUTICALS

9:45  Public Policy Implications for Expanding and Requiring Abuse Deterrence in DEA Schedule II Products

Recent regulatory changes have complicated the development of product analysis from categories I and II to actual abuse deterrent impact. Independent of this effort, Congress is expected to insist on an increased emphasis on abuse deterrence in C-II products. Industry experts need to examine the likelihood that FDA may at some point be pressured to modify its standards for approving ADF formulations for product labeling, including a mandate for all product conversion to an acceptable ADF by a date certain for both “Branded” and “Generic” formulations.

• Examine public policy calls for increased abuse reduction, especially as it relates to non-OxyContin products
• Determine if, from a public policy perspective, attempting to achieve Tier 4 label status is relevant or possible for products without sufficient baseline market share
• Envision how ADF labels as a mandatory public policy objective are viewed as both a laudable and minimally expected goal of Pharma, and how it would contribute to the reduction of C-II product abuse potential

Dan Cohen, Chair, ABUSE DETERRENT COALITION

10:30  Networking Break

11:00  Confront Market and Regulatory Challenges for Patents on Generic Abuse-Deterrent Oxycodone Formulations

Patents for gel-based ADFs for oxycodone do not exist in a vacuum; they are subject to legal and regulatory interpretation. The better you understand the legal standing and opinions that have been raised in these cases, the more you will be prepared to design opioids that have less risk of both addictiveness and legal challenge.

• Scan the history of legal challenges and advances over patented ADFs
• Apply lessons from past legal decisions toward future pipeline decisions

11:45  Innovative Strategies for Measuring Abuse Liability Using Online Data Sources

Although data from Internet forums and other social media is plentiful, it has generally been used anecdotally or to provide case examples. However, with new empirically based approaches, this data can be used to gain a much clearer picture of the aftermarket abuse risk for your drugs. Using social media data streams can allow more in-depth analysis of drug abuse risk factors.

• Rank the relative attractiveness of different prescription drugs for abuse
• Monitor the proliferation of “recipes” for abusing drugs and evading ADFs
• Predict the liking and desirability of low market share opioids or even products not yet on the market

Simon Budman, CEO, INFLEXXION

12:30  Luncheon

1:30  Understand the Significance of Declining Opioid Prescriptions for Your Data Tracking Needs

The opioid marketplace has significantly changed in the last few years, with cultural shifts that overshadow many technical advancements. Doctors are prescribing fewer opioids than market analysts had predicted, mostly out of fear, yet the need for these products has not changed. While this will have major repercussions for the pharma industry, many practitioners don’t know how to look for the most significant trends yet.

• Pinpoint the cause of low abuse rates if drugs are prescribed and sold in low volumes — is it abuse-deterrent or is it simply rare?
• Grasp the implications for making improved label claims if drugs are prescribed less and have fewer patients and data points
• Revamp your postmarketing surveillance and safety data in light of failures of market uptake

Richard Dart, Director, ROCKY MOUNTAIN POISON AND DRUG CONTROL CENTER

2:15  Assess and Improve the Clinical Predictive Value of Preclinical Abuse Potential Models

Most of the physical features of your drug can easily be observed in a clinical setting. But in the case of opioid drug abuse, two critical factors — the results of HAL studies and the drug scheduling assigned by the DEA — only become apparent later. You can avoid unpleasant regulatory surprises by refining and grading the validity of the abuse potential models used in preclinical stages. A recent approach toward validating preclinical models was the first such effort to generate firm data with which to rank their performance, applicability and future uses.

• Statistically analyze each preclinical modeling method’s accuracy in predicting whether a drug will be abused and/or issued a restrictive scheduling tier
• Generate a model-ranking matrix that emphasizes the avoidance of the worst possible outcomes (i.e., an inaccurate preclinical prediction that a drug would not be scheduled)
• Refine predictive models by identifying which are the most effective on each pharmacological class of drugs

David Horton, Principal Scientist, Safety Pharmacology, PFIZER
3:30 **A Consideration of Statistical Analysis Methods for ADFs**

The 2015 guideline on ADFs represents a shift in analysis compared to the reporting of traditional HAL studies. The hypothesis specified in the guideline for primary analysis requires a superiority study design type and testing with abuse-deterrent margins, instead of testing the hypothesis of a comparative design type. Additionally, a secondary responder analysis of percent reduction of effect in an abuse-deterrent product (T), relative to the positive control drug, is now required. A clear understanding of the new analytical methods and reporting requirements for ADFs is necessary for successful submission.

- Apply superiority type hypothesis testing
- Properly grasp implications of sample size choices
- Construct appropriate tables and figures for reporting

*Bijan Chakraborty, Principal Biostatistician, ALGORITHME PHARMA*

4:15 **Exciting Challenges in the Preclinical Abuse Liability Testing of Novel CNS-Active Drug Candidates**

Discovery phase information can help you pre-emptively eliminate compounds with poor developability and reduce unnecessary drug discrimination studies. The high early failure rate of many compounds means an over-reliance on drug discrimination screening puts you at risk for wasting resources before the critical decisions have been made to proceed with a candidate — so well-designed preclinical models are vital for displaying statistical significance at lower drug levels. By properly designing your studies, you can build a framework for convincing comparisons of different abuse-deterrent products and methods.

8:00 Continental Breakfast

**Track A: Abuse Liability Test Design**

- **8:45** Track Chairperson’s Opening Remarks
  *Lorraine Rusch, Ph.D., Vice President, Business Development, VINCE & ASSOCIATES CLINICAL RESEARCH*

- **9:00** Modify Abuse Liability Trial Designs with Greater Versatility for Generic Drugs
  *Lynn Webster, Vice President, Scientific Affairs, PRA HEALTH SCIENCES*

**Track B: Technical Breakthroughs in Abuse Deterrence**

- **8:45** Track Chairperson’s Opening Remarks
  *Joseph Stauffer, CMO, CARA THERAPEUTICS*

- **9:00** Examine the Most Efficient Techniques for Abuse Deterrence
  *Suresh Siddhanti, Senior Director, Clinical Development, NEKTAR THERAPEUTICS*
9:45 | Risk Management and Monitoring Plans to Predict Abuse Potential
Getting the fullest picture of the abuse potential of your drug requires monitoring a diverse array of data through appropriately designed questions and pill-tracking programs. By determining which avenues of abuse are more and less likely, you can make a more convincing presentation to regulatory agencies.
• Remove ambiguity from new pill orders by predicting when refills would normally be requested
• Rank the best pain scales and measuring tools for your questionnaires
• Establish SMQs to seek out adverse events
Lisa Benaise, Head, Office of Medical Safety Evaluation, MITSUBISHI TANABE PHARMA

9:45 | Advance Transdermal Patch Delivery Systems into Abuse Deterrence
Transdermal opioid patches have residual drugs left in them after use, which can be chewed, swallowed or smoked for abuse purposes. This is an underexplored area that needs further development of abuse-deterrent formulations.
• Build from successful ADFs of other delivery routes to reduce risks associated with topical patch abuse
• Add antagonists such as naloxone to patches to block the receptors
• Map the marketing future of both branded and generic ADF patches
Audra Stinchcomb, CSO, F6 PHARMA

10:30 | Networking Break

11:00 | Coordinate Multiple Abuse Data Monitoring Strategies
Oxycodone-based products are subject to very rigid monitoring procedures, tracking prescriptions, purchases and refills. In addition to these systems, you can also utilize indirect, syndromic surveillance of multiple issues in a given population as based on the drug of interest.
• Unite expertise from epidemiologists and safety professionals on each product tracking mission
• Explore focused analyses and other data subsets
• Personalize your surveillance techniques by patient population and treatment regimen
Penny Levin, Director, Global Regulatory Intelligence and Policy, TEVA

11:00 | Analyze the Scientific and Market Potential for Kappa Opioids
Kappa opioids may represent the next breakthrough product in analgesic development. Since these drugs work on the dorsal root ganglion and other peripheral tissues instead of the brain and do not pass the blood brain barrier, they may be less prone to euphoric sensation, and by virtue of their pharmacology have the potential to be less addictive. How viable is this approach for your portfolio?
• Investigate the history of receptor-agonist products
• Compare and contrast oral versus IV delivery routes of kappa opioids
• Forecast the healthcare system’s response to these new products
Joseph Stauffer, CMO, CARA THERAPEUTICS

11:45 | Proper Statistical Foundations for Human Abuse Clinical Trials
Sample sizes and endpoints are just some of the key statistical factors that are associated with the design and analysis of successful human abuse clinical trials. The selection of active controls and the placebo effect are among other factors that can sway trial outcomes.
• Re-envision HAL trial setup based on FDA guidance
• Prepare and account for missing data points
• Focus on the importance of statistical methods in study design
Vincent Yu, Director, Biometrics, UPSHER-SMITH

11:45 | Build Abuse-Deterrent Formulations that Resist Countermeasures
Opioids are not the only prescription drugs in the midst of an arms race between drug companies and drug abusers. The societal cost of clandestine meth labs is enormous. New abuse-deterrent technologies block the extraction and conversion of pseudoephedrine to methamphetamine by meth cooks, which can help slow the growth of this problem.
• Compare and contrast the technical development of meth-resistant technologies
• Analyze the changes in meth consumption after new formulations have hit OTC products
• Discuss the regional effects of meth addiction and the new product uptake rate
Albert Brzeczko, Vice President, Technical Affairs, ACURA PHARMACEUTICALS

12:30 | Luncheon

1:30 | Select Databases and Define Terms to Track Abuse
Retrospective cohort studies can be vital tools for tracking the actual abuse rates of specific drugs and separating their signals from those that are not abused. Proper selection of databases and terms is a must-have first step in evidentiary assessment of the risks of each drug and the successes of ADFs.
• Incorporate distance traveled to account for doctor shopping
• Differentiate between misuse and abuse of prescription drugs
• Scan insurance claim records, EMRs and national data indices
Soledad Cepeda, Director, Epidemiology, JANSSEN

1:30 | Enable Prodrug Solutions to Lower the Abuse Potential for Fast-Release Opioids
While the industry is making progress toward mitigating abuse risks of extended release opioids, the greater challenge comes from avoiding the euphoria of rapid release drugs. The most efficient way of blocking the “high” from a fast-acting opioid is to design a prodrug formulation.
• Engineer opioids with prodrug features that cannot become addictive
• Distinguish between fast-release and extended-release prodrugs
• Stay up to date with the latest advances in prodrug science
Travis Mickle, CEO, KEMPHARM
Preclinical drug safety tests must run the gamut of PK, safety pharmacology, toxicology, and animal dependency and withdrawal symptoms, among others. The broader industry and regulatory interest in clinical and marketing risks for drug abuse means your preclinical tests are more important than ever and must be correctly integrated into a broader testing timeline. Even if you begin to see early-stage clinical adverse events, continuing with animal research will give you a fuller picture of the drug’s properties and behavior.

• Target preclinical animal studies toward improving the design of eventual human abuse potential research
• Rely on specimen pharmacology to choose better comparators
• Keep to the preclinical testing regimen that regulators prefer

Mary Jeanne Kallman, CEO, KALLMAN PRECLINICAL CONSULTING; former Group Leader, Safety Pharmacology, ELI LILLY

New Subcutaneous Formulations to Reduce Oral Drug Abuse

Most ADFs aim to reduce the likelihood of success among drug abusers attempting to crush, snort or inject opioids. However, the most common route of abuse and starting point on the trajectory of addiction is through oral administration. Current guidelines do not address oral drug abuse in detail, so what is the best path forward to reduce the risks?

• Design subcutaneous time-release formulations that eliminate oral supply
• Quantify the benefits of removing physical access to drugs and accidental pediatric dosage risks
• Examine the possible countermeasures for extraction that addicts might employ

Nick Reuter, Manager, Risk Mitigation and Public Policy, RECKITT BENCKISER

“Nearly half of the nation’s 38,329 drug overdose deaths in 2010 involved painkillers like hydrocodone and oxycodone... These narcotics now kill more adults than heroin and cocaine combined, sending 420,000 Americans to emergency rooms each year.”

—The New York Times, April 21, 2014

“Hydrocodone-based painkillers are the most-prescribed pharmacy drugs in the U.S. About 131 million hydrocodone products were dispensed in 2011.”

—Bloomberg News, March 12, 2014

“Across the country, more than 16,000 people died in 2013 from overdoses involving pain medications, and 1 in 20 people in the U.S. age 12 and older reported using prescription pain medicines for nonmedical reasons.”

—Forbes, March 3, 2015
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