Abuse liability workshop
<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dinner</td>
<td></td>
<td>30 min</td>
</tr>
<tr>
<td>Introduction</td>
<td>Marta Sokolowska, PhD</td>
<td>5 min</td>
</tr>
<tr>
<td>FDA Draft Guidance on Assessment of Abuse Potential of Drugs – review of new data</td>
<td>Michael Klein, PhD</td>
<td>5 min</td>
</tr>
<tr>
<td>• Review of the Draft Guidance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Analysis of adverse events:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discussion of adverse events (MedDRA SMQ's) related to abuse and withdrawal</td>
<td>Stephen Sun, MD, MPH</td>
<td>10 min</td>
</tr>
<tr>
<td>Adverse events and pharmacodynamic (subjective) measures - how do they compare?</td>
<td>Kerri Schoedel, PhD</td>
<td>10 min</td>
</tr>
<tr>
<td>• Bipolar vs. unipolar scales, are there situations when one may be more useful than the other?</td>
<td>Kerri Schoedel, PhD / Beatrice Setnik, PhD</td>
<td>15 min</td>
</tr>
<tr>
<td>Premarket assessment of abuse deterrent formulations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Introduction of the new issues addressed in the Draft Guidance on Abuse Deterrent Opioids – Evaluation and labeling</td>
<td>Silvia Calderon, PhD</td>
<td>10 min</td>
</tr>
<tr>
<td>• Three–Tier Approach to the Pre-Market Assessment of the Abuse Deterrent Properties of a Formulation</td>
<td>James M. Tolliver, Ph.D.</td>
<td>15 min</td>
</tr>
<tr>
<td>Discussion</td>
<td>Marta Sokolowska</td>
<td>20 min</td>
</tr>
</tbody>
</table>
Review of the Draft Guidance on Assessment of Abuse Potential of Drugs

Michael Klein, PhD
Director, Controlled Substance Staff
FDA/CDER
The opinions and information in this presentation are those of the FDA contributors and do not necessarily reflect the views and policies of the FDA.
Assessment of Abuse Potential of Drugs

  - Integrates safety information from all areas of the NDA, including brief discussion of abuse deterrence formulations
- FDA Decision Tree (ISCTM February 2012; [http://www.cpdd.org](http://www.cpdd.org))
  - Recommended course of assessment
Abuse Potential Assessment

- Assessing abuse potential is part of the overall assessment of drug safety
- A drug can be scheduled based on its abuse potential, that is, the likelihood that it will be abused after marketing
- Reports of actual abuse not required for scheduling a drug
- Industry would like to know as early as possible if the new drug has abuse potential
- Increase in use and abuse of some pharmaceutical controlled substances
The Ratio of Abuse Related ED Visits are Lower for Oxycodone Combination Products
Goals

• To ensure identification of abuse signals early in development
• To ensure fair playing field
• Preclinical abuse potential data is usually used to provide direction for human studies
  – Positive abuse signals are usually confirmed in human studies
• Appropriate product labeling, drug scheduling and REMS
  – Abuse potential (Section 9 of Labeling)
  – Warnings and precautions
  – Relative risks compared to other products
  – Safe use information of drug
  – Possible risk management strategies
Preclinical screening

- In vitro receptor binding Integrates safety information from all areas of the NDA
- Chemistry
- Animal behavioral pharmacology studies
  - Self administration
  - Drug discrimination
- Impairment studies
- Pharmacokinetics / Pharmacodynamics
Human subject data

- Healthy subjects (Phase 1)
  - Dose range
- Patients (various) (Phase 2 and 3 RCT & OL)
  - Dose range
  - Drug alone
  - With concomitant medications
- Recreational drug abusers (HAPS)
  - Experienced in drug class
Today’s scientific topics

- Systematic collection of adverse events for abuse-related events
- Correlation of adverse events with subjective measures in the human abuse potential study
- Comparison of unipolar and bipolar scales in the human abuse potential study
- Introduction to the new abuse deterrence guidance (January 2013)
- Pre-marketing assessment of abuse deterrence opioid products
Analysis of adverse events:

Discussion of adverse events (MedDRA SMQ's) related to abuse and withdrawal.

Stephen Sun, MD, MPH
20 QUESTIONS - Abuse Potential Assessment Decision Tree (ROADMAP)

1. Chemistry?
2. Binding?
3. Receptor Function?
4. AEs in animals?
5. PK in animals?
6. CNS-active?
7. Effects in animals?
8. Reward effects in animals?
9. Physical dependence in animals?
10. Study plans?
11. Abuse AEs in healthy humans?
12. Abuse AEs in patients?
13. Physical dependence in humans?
14. Human abuse potential study?
15. Reward effects in humans?
16. Abuse AEs in larger patient population?
17. Submission complete?
18. NDA info shows abuse?
19. Reports of actual abuse outside U.S.?
20. Label appropriate?

INVITRO ANIMAL HUMAN ADMIN
Why Accurate Reporting of Abuse-Related Adverse Events Is Important
(Drug Safety’s Telephone Game)

POST-APPROVAL

- Patients
- Attorneys
- HCP
- Industry Reps
- Industry HQ
- Drug Scheduling
- Sponsor advice
- CDER/OND
- CDER/CSS
- FDA; Medwatch Processing Center (Landover, MD)

Pre-Approval

- Investigator’s Brochure (IB)
- Investigator Sites
- Study Subjects
- Study Data Processing
- Sponsor
- CDER/OSE
- CDER/OSE
- Drug Scheduling
- Sponsor advice
- Abuse/Dep PI Review
- Abuse/Dep IB Review

Controlled Substance Staff

- Industry HQ
- Literature
- Approved Product Information (PI)

TAKEAWAY: A high-quality SMQ helps everyone speak a common language (and reduces the variability in translation)
Why Do We Need a MedDRA SMQ for Abuse-Related Events?

1. Provide consistent abuse-related adverse event terms for coding

2. Provide more clarity and precision in communicating the abuse-related adverse events of drugs

3. Allow better and more consistent identification of abuse-related safety signals in clinical trials and postmarketing surveillance
How will the MedDRA SMQ for abuse-related events likely be updated?

1. Identify events that are associated with misuse, abuse, addiction, and diversion

2. Propose new and revise PTs, LLTs

3. Address problematic, overlapping PTs
ADVERSE EVENTS and PHARMACODYNAMIC (SUBJECTIVE) MEASURES

How do they compare?

Kerri A. Schoedel, PhD
Scientific Director, Clinical Pharmacology

Naama Levy-Cooperman, PhD
Megan Shram, PhD
Senior Scientists

INC Research Toronto, Inc.
Disclosure

- Employee of INC Research (performs clinical studies and consulting to pharmaceutical industry)
Adverse Events and Subjective Effects

- Adverse events (AEs) occurring during the treatment phase of clinical studies may provide evidence of mood-elevating, sedative, stimulant or hallucinogenic properties.
- We performed a post-hoc analysis where AE and subjective pharmacodynamic (PD) data were obtained from single-dose, randomized, double-blind crossover 
  abuse potential studies in recreational drug users (19 studies; >400 subjects)
  - Verbatim AE terms were coded using MedDRA® and categorized as:
    • Actual Abuse/Dependence (only 1 event observed)
    • Mood-Elevation
    • Sedation
    • Stimulation
    • Perceptual disturbances
    • (Cognitive impairment)
<table>
<thead>
<tr>
<th>Mood Elevation Effects (ME)</th>
<th>Stimulant Effects (STI)</th>
<th>Perceptual Effects (PER) (Original)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoric mood</td>
<td>Agitation</td>
<td>Abnormal dreams</td>
</tr>
<tr>
<td>Elevated mood</td>
<td>Aggression</td>
<td>Disinhibition</td>
</tr>
<tr>
<td>Feeling drunk</td>
<td>Anxiety</td>
<td>Disorientation</td>
</tr>
<tr>
<td></td>
<td>Energy increased</td>
<td>Dissociation</td>
</tr>
<tr>
<td></td>
<td>Feeling jittery</td>
<td>Feeling abnormal</td>
</tr>
<tr>
<td></td>
<td>Hypervigilance</td>
<td>Hallucination</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>Hallucination, auditory</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>Hallucination, visual</td>
</tr>
<tr>
<td></td>
<td>Nervousness</td>
<td>Hyperaesthesia</td>
</tr>
<tr>
<td></td>
<td>Psychomotor hyperactivity</td>
<td>Hypoaeesthesia</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>Illusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate affect</td>
</tr>
<tr>
<td>Abuse and Dependence Terms (AD)</td>
<td></td>
<td>Mood altered</td>
</tr>
<tr>
<td>Drug dependence*</td>
<td>Apathy</td>
<td>Paraoesthesia</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>Asthenia</td>
<td>Paranoia</td>
</tr>
<tr>
<td>Dependence</td>
<td>Depressed level of consciousness</td>
<td>Psychotic Disorder</td>
</tr>
<tr>
<td>Drug diversion</td>
<td>Fatigue</td>
<td>Sensory disturbance</td>
</tr>
<tr>
<td>Intentional drug misuse</td>
<td>Feeling of relaxation</td>
<td>Thinking abnormal</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>Hypokinesia</td>
<td>Perceptual Effects (PER) (Short-List)</td>
</tr>
<tr>
<td></td>
<td>Indifference</td>
<td>Dissociation</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Hallucination</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Hallucination, auditory</td>
</tr>
<tr>
<td></td>
<td>Sluggishness</td>
<td>Hallucination, visual</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>Illusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sensory disturbance</td>
</tr>
</tbody>
</table>
Mood Elevation AEs
Primarily “Euphoric Mood”

Sedative AEs
Primarily “Somnolence”
Stimulant AEs
Primarily “Hypervigilance” and “Hyperactivity”

Perceptual Disturbances AEs “Short List”
Primarily “Dissociation” (ketamine)
or “Hallucination/Illusion” (zolpidem)
Summary: AE Patterns and SMQs

• With the exception of sedatives, “euphoria” type AEs are observed with high incidence in recreational drug users

• AE patterns associated with drugs of abuse may inform SMQ development:
  – Opioids, cannabinoids: primarily mood elevation with some sedation
  – Ketamine: mood elevation and perceptual disturbances
  – Stimulants: primarily mood elevation and stimulation AEs
  – Sedatives: primarily sedation, relatively low incidence of mood elevation
    • Zolpidem: sedation and perceptual disturbances

• SMQs should balance signal detection against specificity
  – e.g., perceptual disturbance AEs “short list” distinguished ketamine/zolpidem more effectively than longer list
Are Subjects who Report Euphoric Mood AEs also PD “Responders”?

- Abuse potential is evaluated with subjective measures such as “liking” and “high” in recreational drug users
- Examined 8-11 abuse potential studies across all drugs/doses including placebo (~200-300 subjects depending on scale)
  - Pearson Chi square analysis of euphoria AEs (euphoric mood, elevated mood, feeling drunk) vs PD “Responder” at various numerical cut-offs (e.g., \( \geq 65 \), \( \geq 75 \), \( \geq 85 \) on a 100-pt VAS)
- Subjects who reported “euphoria” AEs were significantly more likely to be a PD responder on Drug Liking VAS, High VAS and ARCI MBG (\( p < 0.001 \))
  - False positive rate (subjects who reported euphoria AE but were not PD responders) was usually lower than the false negative rate:
    - Relatively large proportion of subjects who are PD responders don’t report euphoria AEs
  - **Drug Liking** and **High VAS** showed similar rates of false positives and negatives
  - Across a range of values **ARCI MBG** showed a higher rate of false positives but a lower rate of false negatives
  - However, **Dizziness VAS** showed the lowest rate of false positives and false negatives
False positives (Euphoria AE but PD non-responder)
False negatives (PD responder but no euphoria AE)

“Euphoria AE” = Euphoric mood, elevated mood, feeling drunk
Incidence of Euphoric Mood AEs is Significantly Correlated with Median Emax (Peak Effect) of Subjective Scales Across Studies/Drugs/Doses

(Data from 19 studies, with multiple drug classes/doses including placebo. Each point represents data from one drug dose or placebo)

Results for Overall Drug Liking VAS (R=0.632), High VAS (R=0.542) were similar. Correlation was slightly lower for ARCI MBG (R=0.460)
Summary and Conclusions

• This exploratory evaluation indicated that subject-reported AEs are generally consistent with PD results
• AE patterns observed with drugs of abuse may help inform SMQ development
• “Euphoria” AEs are significantly correlated with responses on controlled subjective measures
  — “False negative” rates are relatively high suggesting that AEs are not as sensitive as PD measures
  — “False positive” rates are relatively low but suggest a small subset of subjects may report these AEs but not show a PD response
• AEs may support PD data or evaluate aspects not captured by conventional scales (e.g., adverse effects from snorting)

All subjects were recreational drug users and all studies included eliciting of AEs at regular intervals:

**Incidences and AE-PD patterns may differ in patients or non-drug using volunteer populations**
Consensus on measurements:

Bipolar vs. unipolar scales
- are there situations when one may be more useful than the other?

Beatrice Setnik, PhD
Kerri Schoedel, PhD
Bipolar and Unipolar Scales

- Visual analogue scales (VAS) can be bipolar or unipolar
  - Anchors of bipolar scales represent opposite concepts with neutral in the middle (may or may not have a neutral text anchor)

- Unipolar scales have neutral or no effect at one end
Unipolar and Bipolar Measures

• Bipolar and unipolar scales may have different measurement properties
• Good subject training is essential:
  – However, bipolar scales have “internal” instructional properties (particularly important when subjects are “intoxicated”)
• We’ve performed a post-hoc analysis of data from 18 studies performed at our center using both unipolar and bipolar scales
RANGE OF % CV ACROSS STUDIES
(Including multiple drugs/doses)

Minimum and Maximum Percentage Coefficient of Variation (%CV)

Drug Liking VAS
Overall Drug Liking VAS
Good and Bad Effects VAS**
Good Effects VAS
Bad Effects VAS
Any Effects VAS
High VAS

** Data from only 2 studies
**Pooled PLACEBO Data**  
(18 studies)

<table>
<thead>
<tr>
<th>Measure</th>
<th>N</th>
<th>Mean</th>
<th>Pooled SD</th>
<th>% CV</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bipolar Measures - Neutral=50</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Liking VAS</td>
<td>449</td>
<td>53.4</td>
<td>14.41</td>
<td>27.0%</td>
<td>54.7</td>
</tr>
<tr>
<td>Overall Drug Liking VAS</td>
<td>332</td>
<td>49.7</td>
<td>18.27</td>
<td>36.8%</td>
<td>51.7</td>
</tr>
<tr>
<td>Good and Bad Drug Effects VAS</td>
<td>61</td>
<td>54.9</td>
<td>8.53</td>
<td>15.5%</td>
<td>57.1</td>
</tr>
<tr>
<td><strong>Unipolar Measures - Neutral=0</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High VAS</td>
<td>449</td>
<td>21.4</td>
<td>28.99</td>
<td>135.3%</td>
<td>24.1</td>
</tr>
<tr>
<td>Good Effects VAS</td>
<td>449</td>
<td>28.0</td>
<td>30.89</td>
<td>110.5%</td>
<td>30.8</td>
</tr>
<tr>
<td>Bad Effects VAS</td>
<td>449</td>
<td>17.4</td>
<td>26.13</td>
<td>150.5%</td>
<td>19.8</td>
</tr>
</tbody>
</table>

Placebo response is higher and more variable with unipolar VAS; even within same study.
Bipolar vs. Unipolar Measures
Performance

• Bipolar scales have better measurement properties, particularly for NCEs
  – Variability and placebo response is higher with unipolar measures, though effect sizes for active drugs are similar
  – Variability is much higher with unipolar scales for placebo and drugs with modest effects
• Unipolar scales may be acceptable in some situations
  – Where placebo comparison is less important and no “disliking” is expected
• Generally, studies are powered so that either (or both) will work; however, as a primary assessment bipolar scales may be more reliable
  – More straightforward interpretation in the presence of both good and bad effects
Drug Liking Visual Analog Scale –
A comparison of the Unipolar and Bipolar Scales

Beatrice Setnik, PhD
Pfizer Inc.
ISCTM February 19, 2013
Post Hoc Objectives and Methods

• To compare the unipolar and bipolar Drug Liking Visual Analog Scale (VAS)

  – Study participants received:
    • Cohort 1 (N=19): 40 mg oxycodone immediate release (IR), 40 mg crushed oxycodone extended release (ER)*, 40 and 80 mg intact oxycodone ER, and placebo
    • Cohort 2 (N=16): 20, 40, and 80 mg oxycodone IR, and placebo

• Scales were presented in a fixed order:
  1. Drug Effects Questionnaire (unipolar drug liking VAS # 4 of 10); Do you like the Drug? 0=none; 100=Extremely)
  2. Bipolar drug liking VAS (Do you like the drug effect you are feeling now? 0=Dislike a lot; 50=Neutral; 100=Like a lot).

• Spearman correlation coefficients were calculated for individual VAS scores (for all time points), $E_{\text{max}}$ (peak post-dose score) and $T_{E_{\text{max}}}$ (time to $E_{\text{max}}$) combined and separately for each cohort and treatment.

• Data was obtained from 35 subjects with a total of 2477 values

*oxycodone ER is the previously marketed OxyContin® formulation that is no longer available in the US.
## Results:
### Bipolar vs. Unipolar Drug Liking

Table 1. Unipolar vs Bipolar Drug Liking mean (SD) $E_{\text{max}}$ and expected (calculated) bipolar $E_{\text{max}}$, presented for each treatment (all subjects) and combined (all subjects and treatments)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>treatment group</th>
<th>Drug Liking Emax mean (SD)</th>
<th>“Expected” bipolar $0.5 \times (\text{Uni } E_{\text{max}}) + 50$</th>
<th>Ratio Actual bi/“Expected” bi</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>unipolar</td>
<td>bipolar</td>
</tr>
<tr>
<td>combined</td>
<td></td>
<td>155</td>
<td>47.5 (36.3)</td>
<td>71.9 (16.6)</td>
</tr>
<tr>
<td>cohort 1</td>
<td>40 oxy IR</td>
<td>18</td>
<td>68.5 (25.6)</td>
<td>81.2 (14.2)</td>
</tr>
<tr>
<td></td>
<td>40 oxy CR crush</td>
<td>18</td>
<td>63.4 (23.9)</td>
<td>79.5 (13.2)</td>
</tr>
<tr>
<td></td>
<td>40 oxy CR intact</td>
<td>18</td>
<td>54.6 (32.0)</td>
<td>72.9 (14.5)</td>
</tr>
<tr>
<td></td>
<td>80 oxy CR intact</td>
<td>18</td>
<td>70.4 (23.7)</td>
<td>80.4 (15.5)</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>19</td>
<td>0.0 (0.2)</td>
<td>53.5 (0.8)</td>
</tr>
<tr>
<td>cohort 2</td>
<td>20 oxy IR</td>
<td>16</td>
<td>34.3 (34.5)</td>
<td>68.0 (15.6)</td>
</tr>
<tr>
<td></td>
<td>40 oxy IR</td>
<td>16</td>
<td>62.5 (33.3)</td>
<td>78.4 (15.9)</td>
</tr>
<tr>
<td></td>
<td>80 oxy IR</td>
<td>16</td>
<td>67.1 (27.1)</td>
<td>78.5 (16.3)</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>16</td>
<td>6.9 (18.1)</td>
<td>54.7 (3.9)</td>
</tr>
</tbody>
</table>
Results: Bipolar vs. Unipolar Drug Liking

Scatterplots: Unipolar vs. Bipolar Responses presented for each cohort (all subjects, treatments and time points)

Regression: $Bi = 0.35 \times uni + 50.5$
$R^2 = 51.3\%$

Regression: $Bi = 0.39 \times uni + 53.1$
$R^2 = 74.6\%$
Results:
Bipolar vs. Unipolar Drug Liking

Table 2. Unipolar vs Bipolar Drug Liking correlations for individual VAS scores, $E_{\text{max}}$ and $T_{\text{Emax}}$, presented for each treatment (all subjects and time points*) and combined (all subjects, treatments, and time points*)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>treatment group</th>
<th>individual VAS scores</th>
<th>$E_{\text{max}}$</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>Spearman correlation</td>
<td>n</td>
</tr>
<tr>
<td>combined</td>
<td>combined</td>
<td>2477</td>
<td>0.638</td>
<td>155</td>
</tr>
<tr>
<td>cohort 1</td>
<td>40 oxy</td>
<td>288</td>
<td>0.710</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>40 OC crush</td>
<td>287</td>
<td>0.695</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>40 OC intact</td>
<td>288</td>
<td>0.656</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>80 OC intact</td>
<td>287</td>
<td>0.689</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>303</td>
<td>-0.162</td>
<td>19</td>
</tr>
<tr>
<td>cohort 2</td>
<td>20 oxy</td>
<td>256</td>
<td>0.438</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>40 oxy</td>
<td>256</td>
<td>0.735</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>80 oxy</td>
<td>256</td>
<td>0.685</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>placebo</td>
<td>256</td>
<td>0.093</td>
<td>16</td>
</tr>
</tbody>
</table>

*All time points presented for individual VAS scores; $E_{\text{max}}$ and $T_{\text{Emax}}$ are calculated based on all time points
Results: Bipolar vs. Unipolar Drug Liking

- Among all values (n=2477) there was a positive correlation between bipolar and unipolar ratings (r=0.64).
- A higher correlation (r=0.85) was observed for $E_{\text{max}}$ and a weaker correlation (r=0.23) for $TE_{\text{max}}$.
- Median $TE_{\text{max}}$ showed the greatest differences between measures following treatment with placebo.
- Similar correlations were observed for each cohort.
- Among treatments within each cohort, individual score correlations were higher for oxycodone (0.44 to 0.74) than placebo (-0.16 and 0.09).
Conclusions

• These data suggest a reasonable positive correlation between unipolar and bipolar VAS ratings of drug liking, especially for $E_{\text{max}}$.
• Data interpretation is limited by the use of one study drug, a limited sample size, the fixed ordering of questions, and the use of different verbatim terms in the Drug Liking questions.
• Currently there is no evidence to suggest which scale type is more reliable for assessing drug liking and the use of either scale may be selectively appropriate depending on the study and expected drug effects.
I would gratefully like to thank Dr. Lynn Webster, Principal Investigator and the clinical staff at Lifetree Research who had conducted this study and allowed us to perform this post hoc analysis. This study was funded by King Pharmaceuticals, Inc., which was acquired by Pfizer Inc in March 2011.

I would also like to thank Glenn Pixton (Pfizer Inc) for the statistical analysis of this data and Carl Roland (Pfizer Inc) for data review.
Introduction of the new issues addressed in the Abuse Deterrent Draft Guidance

Silvia Calderon, PhD
How did it come about?

- Congress instructed FDA to promulgate guidance on the development of abuse deterrent products under the Food and Drug Administration Safety and Innovation Act (“FDASIA”)

FDASIA, Pub. L. No. 112-144, 126 Stat. 993, § 1122(c) (2012)

• Provides current thinking
  – Studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties,
  – How those studies will be evaluated by the agency, and
  – What labeling claims may be approved based on the results of those studies

• Science of abuse deterrence is relatively new, and rapidly evolving
  – Flexible approach
Identifies Study “Categories” and Labeling “Tiers”

**Study “Category”**
- Postmarketing Studies
- Clinical Abuse Potential Studies
- Pharmacokinetic Studies
- Laboratory Manipulation and Extraction Studies

**Labeling “Tier”**
- Reduce Abuse in the Community
- Meaningful Reduction in Abuse
- Reduce or Block Effect when Manipulated
- Physicochemical Barriers to Abuse

Strength of Evidence
Additional Research Needs

• Correlation of the PK profile of different opioid formulation with the results of the clinical abuse potential assessment for regulatory purposes

• Identify the best practices to interpret and analyze results from clinical abuse potential studies

• Linking the postmarketing studies with premarket assessment

• Development of postmarketing tools to assess the effect of the formulation in decreasing abuse in the community
Three–Tier Approach to the Pre-Market Assessment of the Abuse Deterrent Properties of a Formulation

James M. Tolliver, Ph.D.
Controlled Substance Staff/CDER/FDA
ISCTM Abuse Liability Workshop
February 19, 2013
Tier 1 - *In Vitro* Manipulation and Extraction Studies

Purpose: To evaluate the ease with which the abuse deterrent mechanism of a product can be defeated

**Mechanical Manipulation** –

Hardness determination using a pharmaceutical apparatus

Use household tools to cut, grade, crush, and grind test formulation *with comparison to reference product*

- Determination of particle size
- Time and ease of manipulation
- Examine impact of first freezing or heating the formulation

**Chemical Extraction**

Evaluate ease of chemical extraction of opioid from test product (intact, crushed, cut and ground) and appropriate reference product(s) For agonist/antagonists formulations this would include isolation of the agonist from the antagonist.

- Extraction Solvents: water, beverages (or simulated beverages), household chemicals, buffers of different pH, and chemicals with different polarities.
- Extraction conducted in presence and absence of agitation and at room and elevated temperature
- Percent opioid extracted is determined at selected time points from a few minutes out to 12 to 24 hours or until opioid is mostly extracted.
Preparation for Intranasal
- Ease of reducing formulation to a particle size for nasal application
- Consider what might happen at lining of nasal cavity - gelling

Preparation for Inhalation
- Ease of manipulating formulation and opioid for smoking
- Base versus the salt
- Vaporization temperature vs. Degradation temperature

Preparation for Intravenous (i.v.) Injection
- Ease in obtaining small volume (1 to 2 mL) with sufficient opioid concentration for i.v. injection
- Considerations of Viscosity - Syringeability and Injectability
Comparison of bioavailability:

- Test product (intact and manipulated) compared to reference ER product (intact and manipulated) and/or reference IR product (generally crushed in solution)
- Swallowed, chewed, snorted product, possibility other routes of administration
- Effects of concomitant food and ethanol intake

Study Design: Open-label, randomized, single-dose, crossover design

Subjects: Healthy adult volunteers under opioid antagonist blockade

Plasma concentrations of opioid, and possibly opioid metabolites, followed as a function of time following dose administration. Specimen collection is done pre-dose and a time points sufficient to cover onset, peak, and offset of the effects of IR and ER products. In the case of agonist/antagonist product formulations, plasma levels of antagonist are also determined over time.
Pharmacokinetic Parameters:

- Peak plasma concentration (Cmax)
- Time to peak plasma concentration (Tmax)
- Area under the concentration versus time curve (AUC_{0-t} and AUC_{0-inf}), relevant partial areas under the curve such as AUC_{0-30 min} or AUC_{0-2 hr}
- Others

Compromise of the release mechanism due to manipulation is indicated when analysis demonstrates:

- Cmax (manipulated) > Cmax (intact) or approaches Cmax of crushed IR
- Tmax (manipulated) < Tmax (intact) or approaches Tmax of crushed IR
- AUC_{0-t} (manipulated) > AUC_{0-t} (intact) or approaches that of crushed IR

Rate of rise of drug concentration is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.
Purpose: Compare subjective effects produced by intact and manipulated test product, intact and manipulated ER reference product and IR reference product.

Study Design: Randomized, placebo-controlled, single-dose, double-blind, crossover design conducted in a controlled setting.

Subjects: Opioid experienced, non-dependent volunteers who have used the intended route of administration (Example: Intranasal abusers for intranasal study).

Route of administration should be based on epidemiological data showing that the selected route is relevant with regard to abuse.

Manipulation technique selected should be based on in vitro test results.

Subjects must past screening phase including naloxone challenge test.

Subjects must past a Pre-Qualification Phase in which subjects must 1) distinguish Drug Liking effects of the reference opioid from placebo; and 2) have an acceptable placebo response; and 3 possibly other requirements.

During the Treatment Phase treatments are administered in a William Square design with appropriate washout periods between treatments depending upon the opioid.

Should include pharmacokinetic evaluation.
Subjective effects, pharmacokinetic parameters and other measures are evaluated just before and as a function of time following treatment.

Subjective Endpoint Measurements – Standardized Questionnaires
- Important primary endpoint is the Drug Liking VAS
- Profile of Mood States

Maximum effect (Emax), time to maximum effect (Tmax) and area under the time-effect curve (AUE$_{0-t}$) are determined along with pharmacokinetic parameters (Cmax, Tmax, AUC$_{0-t}$, etc.).

Statistical Analysis – Need for Statistical Analysis Plan
- Group Statistics – Mean, Median, Standard Error, Interquartile Range
- Individual Responder Analysis
- Increases in Emax and AUE$_{0-t}$ and a decrease in Tmax of manipulated formulation, compared to intact, suggest compromise of the abuse deterrent properties of the formulation.
- Differences in Emax, Tmax and AUE$_{0-t}$ compared to IR formulation is also used to assess compromise of compromise of abuse deterrent properties of the formulation
Thank you