Clinical Assessment of Abuse Deterrence: Pharmacodynamic and Pharmacokinetic Considerations

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Faculty/Presenter Disclosure

- **Faculty:** Megan J. Shram, Ph.D.
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- **Relationships with commercial interests:**
  - Consultant to various pharmaceutical and biotech companies, and clinical research organizations in the area of CNS drug development and abuse liability/abuse deterrence.

- **All information presented is obtained from the public domain**
Overview

- Review of draft Guidance recommendations
  - Pharmacokinetic (PK) studies (Category 2)
  - Clinical (human) abuse potential studies (HAP; Category 3)
- Link between PK and pharmacodynamics (PD) in abuse potential
  - Determinants of variation
  - Case examples
Category 2: Pharmacokinetic Studies

“The goal of the clinical pharmacokinetic studies, Category 2, should be:

- To understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration.

- If food and alcohol alter the pharmacokinetic parameters of the formulation, data should be provided to characterize those effects.”
Category 2: Study Design

- Open-label, randomized, active-controlled, single-dose crossover

- Subject population
  - Healthy volunteers or recreational drug users

- Treatments
  - Intact and manipulated investigational drug
  - Intact and manipulated comparator (ADF or non-ADF, as appropriate)
  - Manipulations based on *in vitro* findings (Category 1)

- Route of administration (ROA)
  - Dependent on epidemiological evidence and ADF technology
  - Typically oral and intranasal (IN), possibly intravenous (IV)

ADF=abuse-deterrent formulation
Category 2: Study Design

- Alcohol interaction
  - “Dose-dumping” of extended-release (ER) formulation in presence of alcohol vs. water
  - In vitro may not always predict in vivo (e.g., Opana® ER)

**In vitro dissolution**

![Graph showing in vitro dissolution](image1)

**In vivo pharmacokinetics**

![Graph showing in vivo pharmacokinetics](image2)

*Fiske et al. (2008) Journal of Pain*
Category 2: Study Design

- Food effect
  - Oral intact and/or manipulated formulation
  - Fasted vs. fed (meal type could vary by formulation)

- Need to determine if food/alcohol effect is related to formulation properties or drug substance itself
  - May require additional study of drug substance alone
Category 2: Endpoints

- PK parameters of interest (parent and active metabolites) include:
  - $C_{\text{max}}$: maximum concentration
  - $T_{\text{max}}$: time to maximum concentration
  - AUC: area under the plasma concentration-time curve
  - pAUC: partial AUC, eg, $\text{AUC}_{0-30\text{min}}$ or $\text{AUC}_{0-2\text{h}}$
  - $T_{1/2}$: terminal elimination half-life

- Adverse events should also be collected as part of these studies, including data on tolerability via different ROA
Category 2: Interpretation

- PK data alone can provide valuable information on ADFs
  - Bioequivalence/bioavailability of manipulated vs. intact formulation
  - Food effect and alcohol “dose-dumping”
  - Comparison to existing marketed ADFs
  - Results can guide design of Category 3 studies (e.g., Remoxy®)
“For drugs with abuse-deterrent properties, the purpose of a clinical abuse potential study is to assess the impact of the potentially abuse deterrent formulation on measures that predict how probable it is that the formulation will be attractive to abusers (“liked”)”
Category 3: Study Design

- Randomized, double-blind, positive- and placebo-controlled, double-dummy, single-dose crossover study

- Subject population
  - Recreational drug users with relevant experience with the ROA
  - Non-physically dependent (confirmed with naloxone challenge)
  - Pharmacologically “qualified”

- Treatments:
  - Investigational drug: manipulated and/or intact formulation (“reference”)
  - Active control, dependent on formulation
    - Active pharmaceutical ingredient (API)
    - Manipulated non-ADF or ADF formulation (IR or ER)
  - Placebo

IR=immediate-release
Category 3: Study Design

- Route of administration and dose
  - Typically oral and IN and if possible, IV
  - Dependent on epidemiology and doses reported to be abused (but safe)
  - Single dose typically sufficient; pharmacology well-characterized

- Blinding: a challenge!
  - ADFs intended to be different and volume/particle size may be deterrent

Vosburg et al., DAD (2012)
Category 3: Measures

- **PD measures**
  - Subjective measures of liking, positive/negative/other effects
    - Visual Analog Scales (bipolar/unipolar)
    - ‘At this moment’ & global assessment
    - ADF specific scales (e.g., nasal irritation)
  - Physiological measures
    - Pupillometry

- **PK sampling**

- **Safety/Tolerability of ADF in intact and tampered form**
Category 3: Analysis and Interpretation

- Change in maximum ($E_{\text{max}}$) liking and other relevant measures vs. active and placebo
  - Mixed effects model for crossover study
  - Responder analysis of Drug Liking (% reduction vs. active)
- Clinically important difference remains to be formally established, though ~10-15 point difference may be meaningful

<table>
<thead>
<tr>
<th>VAS Scale (100 mm-bipolar)</th>
<th>OxyContin (finely crushed)</th>
<th>Original OxyContin (finely crushed)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Liking</td>
<td>Mean (SE) 80.4 (3.9)</td>
<td>94.0 (2.7)</td>
<td>13.6 (15.6%)</td>
</tr>
<tr>
<td></td>
<td>Median (Range) 88 (36-100)</td>
<td>100 (51-100)</td>
<td>12 (12.8%)</td>
</tr>
<tr>
<td>Take Drug Again</td>
<td>Mean (SE) 64.0 (7.1)</td>
<td>89.6 (3.9)</td>
<td>25.6 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>Median (Range) 78 (0-100)</td>
<td>100 (20-100)</td>
<td>22 (24.7%)</td>
</tr>
</tbody>
</table>
Category 3: Analysis and Interpretation

- Change in maximum ($E_{max}$) liking and other relevant measures vs. active and placebo
  - Mixed effects model for crossover study
  - Responder analysis of Drug Liking (% reduction vs. active)
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<table>
<thead>
<tr>
<th>Drug</th>
<th>Abusing* Original OxyContin Before (%) (July ‘09 to Aug ‘10)</th>
<th>Abusing reformulated OxyContin After (%) (Aug ‘10 to Mar ‘12)</th>
<th>Change in Abuse (%)</th>
<th>p-value for change</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin</td>
<td>23.7</td>
<td>12.1</td>
<td>-49</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>- OxyContin orally</td>
<td>12.4</td>
<td>9.0</td>
<td>-27</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>- OxyContin by injecting, snorting or smoking</td>
<td>17.8</td>
<td>5.2</td>
<td><strong>-71</strong></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ER oxymorphine</td>
<td>1.9</td>
<td>5.5</td>
<td>+196</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ER morphine</td>
<td>5.4</td>
<td>4.7</td>
<td>-12</td>
<td>0.0209</td>
</tr>
</tbody>
</table>

Black et al. APS (2012); Coplan (2013)
PK-PD Analysis in Category 3

Draft guidance (January 2013):

- “PK data should be collected to correlate with the PD outcomes.”
- “The rate of rise of drug onset for the intact and manipulated potentially abuse-deterrent formulation should be given appropriate weight in the overall analysis of the abuse deterrent properties.”

Goal of PK-PD analysis is to assist in predicting the effect of a drug over time in relation to exposure

- Implications for development of generic ADFs
What is “quantitative link between changes in the pharmacokinetics of opioids in different formulations and results of a clinical abuse potential study with those same formulations”?

*Can PK accurately predict PD?*
PK-PD: Determinants of Variation

System
- Age
- Gender
- Opioid experience
- Tolerance/Dependence
- Expectations
- Genetic variations

Pharmacodynamics
(CV ≈50- >100%)
- Subjective effects
- Miosis
- Analgesia
- Respiratory depression
- Adverse events
- Behavior

Pharmacokinetics
(CV ≈30%)
- Opioid, Dose
- Formulation, Route
- BBB permeability
- ADME, protein binding
- Active metabolites
- Plasma vs. Effect site
- Arterial v venous sampling/timing

?? Endpoints Analysis Interpretation

CV=coefficient of variation
When PK/PD relationship might exist

- Physicochemical barrier
  - Resistance to manipulation for oral, IN and IV administration
- Prodrug
  - Must be cleaved systemically to liberate active moiety
  - Deterrence from IN and IV administration, and possibly oral if limited by saturable process
- Delivery System
  - Modified drug delivery to reduce diversion via multiple routes
Rate of Rise: “Abuse Quotient”

• Lower $C_{\text{max}}$ and longer $T_{\text{max}} \rightarrow$ lower “Abuse Quotient”

Oxycodone Pharmacokinetics

Drug Liking Visual Analog Scale

OC=original OxyContin®; OTR=reformulated OxyContin®
When PK-PD relationship might exist

Effects unrelated to drug exposure can impact subject’s drug experience (at the moment and overall)

Data presented at ADF meeting (2013); Harris et al. (2014)
Subjective vs. Physiological

**$E_{\text{max}}$ of Drug Liking**

- Overall $R^2=0.12$

**Maximum Miosis**

- Overall $R^2=0.27$

- Limited, weak relationship for subjective measures and exposure

- OTR fine
- OTR coarse
- OC fine
When PK-PD might matter less

- Opioid agonist-antagonist combinations
  - Antagonist attenuates/reverses effect of opioid
- Aversion technology
  - Aversive agent not intended to impact exposure to agonist
  - Might still experience high from opioid; however, product not liked

Colucci et al. (2013)
Category 2/3 Studies: Impact on labeling

- Category 2 studies described in label, e.g., alcohol interaction on drug release and effect of food
  - Seen in many labels, prior to Guidance

- Category 3 studies may achieve route-specific Tier 3 claim and/or summary of study results in label
  - Label claim and results: OxyContin®, Targiniq®, EMBEDA®
  - Results (implicit claim): Oxecta®
Conclusions

- PK can be used to determine impact of food and alcohol on exposure to ADF, but PK alone is not expected to adequately characterize or predict abuse deterrence.
- HAP study results can provide the most predictive pre-market evidence of abuse deterrence:
  - As conducted to assess abuse potential of new chemical entities for decades.
- PK-PD relationship in abuse potential is weak and highly variable:
  - May depend on the abuse-deterrent mechanism under study.