Evaluation of ADF Opioid Drug Products
Challenges, innovations and current practices related to evaluation of ADF opioid drug products

Lynn Webster, MD
Vice President of Scientific Affairs
PRA Health Sciences
Salt Lake City, UT
WebsterLynn@prahs.com
Twitter: @LynnRWebsterMD
www.LynnWebsterMD.com
Disclosures

- Alcobra
- BDSI
- Bonti
- Charleston Labs
- Daiichi Sankyo
- Depomed
- Egalet
- Indivior
- Inspirion
- Insys
- Kempharm
- Mallinckrodt
- Pain Therapeutics
- Pfizer
- Pernix
- Shionogi
- Teva
- Trevena
- Trevi
Abuse Deterrent Definition

• Pharmaceutical product is formulated so its physical or chemical properties may reduce, deter or prevent abuse

• Changes impart properties that make extraction and purification of the active component difficult for abuse by another route

• Changes in the formulation might prevent inadvertent overdoses that can come about by chewing or cutting tablets to facilitate swallowing

• For “abuse deterrent” products to be an effective approach to reducing drug abuse, their development would have to apply to all drug products on the market: innovator and generic products
“Labeling is the first tool the Food and Drug Administration is looking at to incentivize the development of successful abuse-deterrence Opioids.”

Douglas Throckmorton, MD,
Deputy Director for Regulatory Programs
FDA’s Center for Drug Evaluation and Research
# FDA Guidance on Abuse-deterrent Opioids

## Study Categorization and Abuse-Deterrent Label

<table>
<thead>
<tr>
<th>Study Categories</th>
<th>Premarketing Studies</th>
<th>Post Marketing Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Preclinical in vitro manipulation and extraction studies</td>
<td></td>
</tr>
<tr>
<td>Category 2</td>
<td>Pharmacokinetic (PK) studies</td>
<td></td>
</tr>
<tr>
<td>Category 3</td>
<td>Clinical abuse potential (e.g., drug liking) studies</td>
<td></td>
</tr>
<tr>
<td>Category 4</td>
<td>Epidemiological studies measuring abuse deterrence (overall and route-specific abuse and abuse deterrence)</td>
<td></td>
</tr>
</tbody>
</table>

## Tiers for Potential Abuse-Deterrent Claims

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
<th>Tier 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>The product is formulated with physicochemical barriers to abuse</td>
<td>The product is expected to reduce or block effect of the opioid when the product is manipulated</td>
<td>The product is expected to result in a meaningful reduction in abuse</td>
<td>The product has demonstrated reduced abuse in the community</td>
</tr>
</tbody>
</table>

---

**Abuse-Deterrent Opioids — Evaluation and Labeling**

Guidance for Industry

Additional topics are available from:

Office of Communications
Division of Drug Information, WDC1, Room 2311
Silver Spring, MD 20920-8235
Phone: 301-796-9000, Fax: 301-487-8714
druginfo@fda.hhs.gov

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm127873.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Clinical Medical April 2015
# Mechanisms of abuse deterrence

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical/chemical barriers (may not deter all of these)</td>
<td>Prevent chewing, crushing, cutting, grating, or grinding (physical barrier) Impede extraction of opioids with common solvents (chemical barrier)</td>
</tr>
<tr>
<td>Agonist/antagonist combinations</td>
<td>Addition of a sequestered or non-sequestered opioid antagonist</td>
</tr>
<tr>
<td>Aversion</td>
<td>Component(s) added that produces an unpleasant effect after manipulation, after administration by alternate routes (e.g. mucous membrane irritant), or if used at doses higher than indicated</td>
</tr>
<tr>
<td>Delivery system</td>
<td>Long-acting injectable or depot formulations that are difficult to manipulate</td>
</tr>
<tr>
<td>Prodrugs or new molecular entities</td>
<td>Require chemical or enzymatic transformation \textit{in vivo} to active drug; may have inherent pharmacodynamic or pharmacokinetic properties that lower abuse potential</td>
</tr>
<tr>
<td>Combination of technologies</td>
<td>Contain greater than 2 of the other defined technologies</td>
</tr>
<tr>
<td>Novel approaches</td>
<td>Technologies that are not characterized by one of the defined categories (e.g. technology that provides protection against multiple-pill overdose)</td>
</tr>
</tbody>
</table>

Stages of Human Abuse Potential (HAP) Studies

- Screening
- Discrimination
- Study
- Analysis
Stages of HAP Studies: Screening

**Screening**
- IRB
  - Does the IRB understand HAP?
    - Consent
    - Confidentiality
    - Compensation

**Discrimination**
- Recruitment
  - Gender (sex)
  - Age
  - Ethnicity
  - Social

**Study**
- Population
  - How experienced
  - Route of exposure
  - Poly substances
  - Tobacco
  - Marijuana

**Analysis**
Stages of HAP Studies: Discrimination

- **Screening**
  - Training Subjects
    - Understanding tests
    - Expectations
    - Reproducibility
    - Anticipation

- **Discrimination**
  - Discrimination Criteria
    - Placebo response
    - Active control
    - Emax window
    - Dose
    - Dosages (arms)

- **Study**

- **Analysis**
  - Discrimination Criteria (continued)
    - Bipolar Scale
    - Active > Placebo
    - Placebo
      - <60, >40
Stages of HAP Studies: Study

- **Screening**
- **Discrimination**
- **Study**
- **Analysis**

**Pharmacy Challenges**
- Drug preparation
  - Manipulation
  - Encapsulation
- Blinding
- Routes of Administration

**Manipulation Technique**
- Degree of effort
- Method of manipulation
- Time

**Assessment Tools**
- Scales
- Number of scales
- Cognitive
- Paper vs electronic
- Unipolar vs bipolar
Stages of HAP Studies: Study

- Screening
- Discrimination
- Study
- Analysis

Blinding
- Particle size/volume
- Irritation
- Smell & taste
- Visual
- Texture
- Consistency

Blinding (continued)
- Color difference
- Blinding solution
- Placebo utilized
- Blinding method during dosing

Endpoints
- Maximum Effect ($E_{\text{max}}$)
- AUE
- Abuse quotient (A/Q)
Rate of Rise May Contribute to Differential Abuse Potential

- Category 2 PK data intended to measure ‘rate of rise’, peak and early concentrations, as measured by
  - Early concentrations and partial AUCs
  - $C_{\text{max}}$ and $T_{\text{max}}$
  - $C_{\text{max}} / T_{\text{max}}$ ratio (“Abuse Quotient”)

Webster, 2015.
Key Assessments

- Subjective Abuse Liability Assessments
  - Bipolar VAS
    - Drug Liking
    - DEQ
  - Unipolar VAS
    - Drug High
    - DEQ

<table>
<thead>
<tr>
<th>Unipolar VAS</th>
<th>None</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you like the drug?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bipolar VAS</th>
<th>Dislike a lot</th>
<th>Like a lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you like the drug effect you are feeling now?</td>
<td></td>
<td>Neutral</td>
</tr>
</tbody>
</table>
Example of Individual Discrimination Data & Interpretation

Pass - Responder

Fail - Placebo Responder

Fail - Unable to Tolerate

Fail - Non-Responder
Stages of HAP Studies: Study

- Screening
- Discrimination
- Study
- Analysis

- Significances
  - Statistical
  - Clinical
Take Drug Again Scores following Intranasal Administration in Selected HAP Studies of Opioid ADFs

Hansen, E., He, J., Webster, L., Turncliff, R. Considering “Take Drug Again” as the Primary Endpoint in Clinical Studies of Abuse Deterrent Formulations. Poster session presented at: annual meeting of the College on Problems of Drug Dependence; 2018; San Diego, California.
TDA Sample Size Calculations

Hansen, E., He, J., Webster, L., Turncliff, R. Considering “Take Drug Again” as the Primary Endpoint in Clinical Studies of Abuse Deterrent Formulations. Poster session presented at: annual meeting of the College on Problems of Drug Dependence; 2018; San Diego, California.
Overdose Protection ADFs

Average Change in Oxygen Saturation

Difference in Respiratory Slope at One Hour Post Dose

Overdose Protection ADFs

Time-Matched Average Respiratory Results of Subjects

<table>
<thead>
<tr>
<th>Results at 60 min post dose</th>
<th>Placebo</th>
<th>30 mg Oxycodone</th>
<th>LS Mean Difference (95% CI)</th>
<th>Resultant Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>S – Slope of Regression (MV vs. ETCO₂)</td>
<td>2.28</td>
<td>1.13</td>
<td>-1.15 (-2.08, -0.23)</td>
<td>50%</td>
</tr>
<tr>
<td>MV – Minute Ventilation (L/min)</td>
<td>20.81</td>
<td>15.13</td>
<td>-5.68 (-9.56, -1.82)</td>
<td>27%</td>
</tr>
<tr>
<td>R – Ratio of MV/ETCO₂ (L/min/mmHg)</td>
<td>0.44</td>
<td>0.30</td>
<td>-0.14 (-0.23, -0.5)</td>
<td>31%</td>
</tr>
<tr>
<td>RR – Respiration Rate (Breaths/min)</td>
<td>12.7</td>
<td>12.9</td>
<td>0.2 (-3.86, 3.44)</td>
<td>2%</td>
</tr>
<tr>
<td>ETCO₂ – End-tidal CO₂ (mmHg)</td>
<td>47.9</td>
<td>51.4</td>
<td>3.5 (1.2, 5.8)</td>
<td>7%</td>
</tr>
</tbody>
</table>

L Webster et. al. Oxycodone Effect on Ventilatory Drive.  
https://www.cdc.gov/media/releases/2018/p0329-drugoverdose-deaths.htm
What’s next?

• Pharmacokinetic measurements for generic ADFs as surrogates for HAP
• Develop statistical analysis that is proven to have clinical meaningfulness
• Develop accepted endpoints for emerging overdose protection technology
Thank you!

Follow me on Twitter: @LynnRWebsterMD

www.LynnWebsterMD.com