Foundations of Pharmacokinetic Comparisons of Generic Opioids to RLDs with Labeling Describing Abuse-Deterrent Properties

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Public Meeting on Pre-market Evaluation of AD Properties of Opioid Drug Products
October 31st, 2016
General Principles for Evaluating the Abuse Deterrence of *Generic* Solid Oral Opioid Drug Products (2016 Draft)

• If the RLD’s labeling describes properties that are expected to deter misuse or abuse, the potential ANDA applicant should evaluate its proposed generic drug product in comparative in vitro studies and, in some cases, in relevant pharmacokinetic or other studies to show that it is no less abuse-deterrent than the RLD with respect to all potential routes of abuse.

• FDA intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic solid oral opioid drug product.
General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (2016 Draft)

• PK studies as mentioned in guidance should be conducted to ensure the absence of significant difference in the rate and extent of absorption

• Comparative abuse-potential studies are generally not necessary, except in certain circumstances: e.g., comparing the abuse deterrence potential of an excipient that functions as an aversive agent.
Deterrence of Abuse by Insufflation in All ADF Opioid Product Labels

<table>
<thead>
<tr>
<th>NDA</th>
<th>API</th>
<th>Firm</th>
<th>Brand</th>
<th>Approval</th>
<th>Dosage Form</th>
<th>Abuse Deterrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>206627</td>
<td>Hydrocodone</td>
<td>PURDUE</td>
<td>Hysingla ER</td>
<td>11/20/14</td>
<td>ER Tablet</td>
<td>Oral, IN</td>
</tr>
<tr>
<td>208090</td>
<td>Oxycodone</td>
<td>COLLEGIUM</td>
<td>Xstampza ER</td>
<td>04/26/16</td>
<td>ER Capsule</td>
<td>IN</td>
</tr>
<tr>
<td>022272</td>
<td>Oxycodone</td>
<td>PURDUE</td>
<td>OxyContin</td>
<td>04/05/10</td>
<td>ER Tablet</td>
<td>IN</td>
</tr>
<tr>
<td>206544</td>
<td>Morphine</td>
<td>INSPIRION</td>
<td>MorphaBond</td>
<td>10/02/15</td>
<td>ER Tablet</td>
<td>IN</td>
</tr>
<tr>
<td>207621</td>
<td>Oxycodone/Naltrexone</td>
<td>PFIZER</td>
<td>Troxyca ER</td>
<td>08/19/16</td>
<td>ER Capsule</td>
<td>Oral, IN</td>
</tr>
<tr>
<td>205777</td>
<td>Oxycodone/Naloxone</td>
<td>PURDUE</td>
<td>Targiniq ER</td>
<td>07/23/14</td>
<td>ER Tablet</td>
<td>IN, IV</td>
</tr>
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<td>022321</td>
<td>Morphine/Naltrexone</td>
<td>PFIZER</td>
<td>Embeda</td>
<td>08/13/09</td>
<td>ER Capsule</td>
<td>Oral, IN</td>
</tr>
</tbody>
</table>

As of 10/20/2016

IN: intranasal
Draft Guidance Decision Tree

For products with abuse deterrent claims by insufflation, applications quickly get to PK studies.

In vitro characterizations of physicochemical properties cannot predict in vivo PK profile of nasal powder.
Nasal PK Study in Current Draft Guidance

• PK study as mentioned
  – In healthy volunteers incorporating naltrexone to block the PD effects of opioids
  – Cmax, Tmax, AUC and pAUCs (when applicable) for opioid API and any active metabolites
  – Statistically significant difference in profiles

• Revisions to discuss today
  – Population should be experienced nasal abusers
  – Confidence interval criteria
  – When comparing R and T, the same level of mechanical or chemical manipulation to maximize the availability of R and T should be applied prior to administration through the proposed route
  – Questions via OGD control correspondence process
Other Routes Where PK Studies are Relevant

• For discussion today (Oral Route)
• For single API products with oral abuse deterrence claims when in vitro testing is not sufficient (eg, by chewing)
• Agonist/antagonist combinations:
  – All active ingredients (e.g. Oxycodone/Naltrexone) should be measured in the BE PK studies on intact products
  – PK studies to confirm oral absorption of sequestered actives after manipulation will be recommended in product specific guidance if needed
Standard BE Assessment for Generic Products

• Study Design:
  – Single-dose, two-way crossover, fasted + fed
  – Alternatives: Single dose parallel (fasted), single dose replicate, multiple dose two way cross over (fasted), clinical endpoint study

• Statistical Analysis:
  – 90% Confidence Intervals (CI) must fit between 80%-125%
PK Evaluations: Cmax, AUC, and Rate of Rise of the Initial PK Profile

• Evaluations on Cmax and AUC may not be sufficient
  – Conventional BE assessment typically based on Cmax and AUC following single dose

• FDA exploring relationships between PK metrics and abuse deterrence in terms of VAS (visual analogue scale) including rate of rise of the initial PK profile
  – Focus is on relationship between PK metrics and VAS
  – Abuse deterrence can be correlated to the rate of drug onset
  – Equivalence in AUC and Cmax do not ensure similar rate of rise in the initial part of the PK profile
PK Evaluations: Partial AUC

• Partial AUC (pAUC) is the metric OGD uses when the drug exposure within certain time period is clinically meaningful
  – For abuse deterrence, the initial drug exposure is important and pAUC can be used as a measure of rate of drug onset

• How to select pAUC
  – The relationship between PK variable and PD endpoints of clinical significance can be used to identify the most appropriate pAUC
  – Recommendations of pAUC can be API/product-specific

• Intent to identify pAUC as PK metric has motivated further research on PK-PD relationships based on data currently available
Endpoints for Drug Liking and Abuse Deterrence from Clinical Studies

PD endpoints commonly measure include:

**VAS**: take drug again, drug liking, overall drug liking, high VAS, good effects, and any effect.

ARCI MBG Scale (euphoria), ARCI PCAG (sedative), and Pupillometry

2015 Guidance Abuse-Deterrent Opioids Evaluation and Labeling

“The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse”.

The Agency considers VAS to be the most important endpoint in assessing the clinical relevance of the abuse-deterrent effects of a product
Case Example:
Hysingla ER Tablet
(hydrocodone bitartrate)

FDA has determined that this product has abuse-deterrence properties which are expected to deter intranasal abuse, oral abuse when chewed, and intravenous abuse.
### Clinical PK/Abuse Deterrence Studies for Hydrocodone

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Hysingla ER Hydrocodone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>HYD1013</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Study</strong></td>
<td>Randomized, double-blind, placebo-controlled, crossover study</td>
</tr>
<tr>
<td><strong>Subject</strong></td>
<td>35</td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>A: API Solution 60 mg</td>
</tr>
<tr>
<td></td>
<td>B: HYD 60 mg intact</td>
</tr>
<tr>
<td></td>
<td>C: HYD 60 mg chewed</td>
</tr>
<tr>
<td></td>
<td>D: HYD 60 mg milled</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td>Take drug again VAS, Drug Liking VAS, Overall drug liking VAS, High VAS, Good effects VAS, Any effect VAS, ARCI MBG Scale (euphoria), ARCI PCAG (sedative), and pupil size</td>
</tr>
</tbody>
</table>
Hydrocodone PK Profiles
ADF vs non ADF, Intact vs Manipulated

• In comparison to the positive controls (API solution or powder), ADF has lower Cmax and longer Tmax
• Manipulated tablet has higher Cmax and shorter Tmax than intact tablet
• Changes in AUC$_{0\text{-}\text{last}}$ are less prominent following oral route of administration
Hydrocodone PK-PD Profiles: Oral

Maximum Take Drug Again VAS (Emax) from Oral Route

<table>
<thead>
<tr>
<th>Treatments</th>
<th>API Solution</th>
<th>HYD Intact</th>
<th>HYD Chewed</th>
<th>HYD Milled</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>89.7 (21.2)</td>
<td>34.3 (36.0)</td>
<td>44.3 (40.8)</td>
<td>84.1 (28.1)</td>
<td>3.9 (15.9)</td>
</tr>
</tbody>
</table>
Hydrocodone PK-PD Profiles: Intranasal

Maximum Take Drug Again VAS (Emax) from Intranasal Route

<table>
<thead>
<tr>
<th>Treatments</th>
<th>API Powder</th>
<th>HYD Fine</th>
<th>HYD Coarse</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>85.2 (24.9)</td>
<td>40.7 (38.4)</td>
<td>36.4 (41.0)</td>
<td>2.0 (10.0)</td>
</tr>
</tbody>
</table>
Conclusions

• For the hydrocodone abuse deterrent product
  – Drug liking VAS curves follow a similar pattern as observed in PK curves
  – Based on take drug again VAS, the manipulated products show less abuse potential than control for the routes of abuse deterrent property as described in its labeling (ie, intranasal route and oral abuse when chewed)
  – PD endpoints have higher variability

• Ongoing internal assessment to quantitatively explore the relationship between PK metrics and PD endpoints including take drug again VAS for other opioid APIs with abuse deterrent formulations
Summary of Guidance Regarding Use of PK Data

• PK studies are important for products with abuse-deterrent claims
  – For Agonist/Antagonist combinations: PK studies to confirm oral absorption of sequestered actives after manipulation will be recommended in product specific guidance

• PK studies are generally expected for abuse deterrent claims
  – By insufflation and
  – By ingestion when in vitro testing is not sufficient
Acknowledgement

• **OGD**
  - Data Analysis:
    – Zhichuan (Matt) Li PhD
    – Yehua (Josh) Xie PhD
    – Xiaoyan Yang PhD
    – Lanyan (Lucy) Fang PhD
    – Myong-Jin Kim PharmD
    – Robert Lionberger PhD
  - Other members for general guidance development

• **OCP/OTS**
  – Srikanth Nallani PhD

• **OND**
  – Sharon Hertz MD

• **The Workshop Planning Team**
• **The CDER Opioids Task Force**
Clinical PK/Abuse Deterrence Studies Available for PK – PD Relationships For Single API Products: Hydrocodone, Oxycodone, and Morphine

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<td>HYD1014</td>
<td>OXYDET-21</td>
<td>OTR-1018</td>
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<td>Arms</td>
<td>A: API Solution 60 mg</td>
<td>A: API 60 mg</td>
<td>A: DETERx 40 mg</td>
<td>A: OTR 30 mg fine</td>
</tr>
<tr>
<td></td>
<td>B: HYD 60 mg intact</td>
<td>B: HYD 60 mg fine</td>
<td>B: DETERx 40 mg</td>
<td>B: OTR 30 mg</td>
</tr>
<tr>
<td></td>
<td>C: HYD 60 mg chewed</td>
<td>C: HYD 60 mg intact PO</td>
<td>C: OC IR 40 mg</td>
<td>C: OC 30 mg fine</td>
</tr>
<tr>
<td></td>
<td>D: HYD 60 mg milled</td>
<td>D: HYD 60 mg coarse</td>
<td>D: API powder 30 mg</td>
<td>D: API powder 30 mg</td>
</tr>
<tr>
<td></td>
<td>E: Placebo</td>
<td>D: Placebo</td>
<td>E: Placebo</td>
<td>E: Placebo</td>
</tr>
<tr>
<td></td>
<td>A: IDT-001 60 mg crushed</td>
<td>B: IDT-001 60 mg intact</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: MS Contin 60 mg</td>
<td></td>
<td></td>
</tr>
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