Prediction of Human Pharmacokinetics Utilizing In Vitro Chewing Method and Physiologically Based Pharmacokinetic (PBPK) Analyses for Abuse-Deterrent Hydrocodone Bitartrate Extended Release Tablets

Workshop: Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls
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Disclaimer

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Outline

1. Background
   A. Opioid Crisis
   B. Abuse Deterrent Formulation (ADF)

2. Case Study: Hydrocodone Extended Release Tablets
   A. In Vivo Chewing and Dissolution method
   B. Application of PBPK model to predict in vivo behavior of impact of different types of physical manipulation e.g., crushing, chewing or administered as intact tablet
   C. Product-Specific Guidance
   D. Potential Application
Drug Overdose Deaths by State, US 2017

- Drug overdose deaths continue to increase in the United States.
- From 1999 to 2017, more than 702,000 people have died from a drug overdose.
- Serious public health issue.

Abuse Deterrent Formulation

- Deterrence to abuse potential achieved via several mechanisms e.g., physical/chemical barrier, agonist/antagonist, prodrug etc.

- Development of abuse deterrent formulation is one of several steps to fight this epidemic.

- FDA approved several abuse deterrent opioid formulations.
# Opioid ADF Approvals

<table>
<thead>
<tr>
<th>NDA #</th>
<th>API</th>
<th>Trade Name</th>
<th>Approval date</th>
<th>Dosage Form</th>
<th>Labeling for Abuse Deterrence</th>
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<tbody>
<tr>
<td>022272</td>
<td>Oxycodone</td>
<td>OxyContin</td>
<td>04/05/10</td>
<td>ER Tablet</td>
<td>IV, IN</td>
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<tr>
<td>022321</td>
<td>Morphine/Naltrexone</td>
<td>Embeda</td>
<td>10/17/14</td>
<td>ER Capsule</td>
<td>IN, Oral (crushed)</td>
</tr>
<tr>
<td>206627</td>
<td>Hydrocodone</td>
<td>Hysingla ER</td>
<td>11/20/14</td>
<td>ER Tablet</td>
<td>IV, IN, Oral (chewed)</td>
</tr>
<tr>
<td>206544</td>
<td>Morphine</td>
<td>MorphaBond ER</td>
<td>10/02/15</td>
<td>ER Tablet</td>
<td>IV, IN</td>
</tr>
<tr>
<td>208090</td>
<td>Oxycodone</td>
<td>Xtampza ER</td>
<td>04/26/16</td>
<td>ER Capsule</td>
<td>IV, IN</td>
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<td>208603</td>
<td>Morphine</td>
<td>Arymo ER</td>
<td>01/9/2017</td>
<td>ER Tablet</td>
<td>IV, IN</td>
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<tr>
<td>209777</td>
<td>Oxycodone</td>
<td>RoxyBond</td>
<td>04/20/2017</td>
<td>Tablet</td>
<td>IV, IN</td>
</tr>
</tbody>
</table>

IV: intravenous; IN: intranasal
Abuse Deterrence via Chewing Route

• Chewing extended-release opioid tablets prior to ingestion is one of several methods used by drug abusers to disable the extended release mechanism of the tablet with the goal to achieve high opioid plasma concentrations (Cmax) within a short period of time (Tmax).

• Research project aimed at developing an in-vitro chewing method which can predict in-vivo opioid availability following chewing of opioid ER tablets.
Development of an In Vivo Predictive Method for Determining Opioid Availability Following Chewing of Solid Oral Opioid Drug Products

• **Objective:** To develop an in vitro chewing method which can predict in vivo opioid availability following chewing of opioid drug products.

• **Impact:**

  – Can be a useful tool for generic/new ADF product development

  – Can be recommended in product-specific guidance as an in vitro option in lieu of currently recommended in vivo chewing studies if the in vitro method can be sufficiently validated.
Case study: Hydrocodone Bitartrate Extended Release Tablet

- Hydrocodone bitartrate ER tablet was recognized by FDA as having abuse-deterrent properties that are expected to deter misuse and abuse via chewing.

Hydrocodone bitartrate 60 mg ER Tablets
In Vitro Chewing Method for Determining Opioid Availability Following Chewing

- Tablets are placed between two chewing jaws
- Chewing process consists of up and down strokes of the lower jaw and a shearing (twisting) movement of the upper jaw

<table>
<thead>
<tr>
<th>Test conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>37±0.5°C</td>
</tr>
<tr>
<td>Chewing frequency (cycles/min)</td>
<td>40</td>
</tr>
<tr>
<td>Twisting angle (degree)</td>
<td>20°</td>
</tr>
<tr>
<td>Gap between the jaws (mm)</td>
<td>4.3 mm</td>
</tr>
<tr>
<td>Media type</td>
<td>Artificial saliva at pH 6.8</td>
</tr>
<tr>
<td>Media volume</td>
<td>40 mL</td>
</tr>
<tr>
<td>Pre-warming time</td>
<td>10 min</td>
</tr>
<tr>
<td>Chewing force</td>
<td>≈ 400 N</td>
</tr>
</tbody>
</table>

Hydrocodone bitartrate ER tablets at 60 mg

Erweka DRT 3 chewing apparatus

FDA-recommended dissolution method
(USP I, 100 rpm, 900 mL SGF pH 1.2)


FDA Dissolution Methods: [https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm](https://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults.cfm)

PSG: [https://www.accessdata.fda.gov/drugsatfda_docs/psg/Hydrocodone%20bitartrate_oral%20ER%20tablet_NDA%20206627_RV07-18.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/psg/Hydrocodone%20bitartrate_oral%20ER%20tablet_NDA%20206627_RV07-18.pdf)
In Vitro Release Results

Dissolution

- Chewed
- Crushed
- Intact

Time (Hour) vs. Label Claim Release (%)


www.fda.gov
Mean Plasma Hydrocodone Concentration After Administration of Hydrocodone Solution and Intact, Crushed, Chewed and Intact form of Hydrocodone Bitartrate ER Tablet

- Single-center, double-blind, randomized, crossover study
- Non-dependent recreational drug users with moderate experience with opioids
Model Development and Validation

Hydrocodone Solution
60 mg
PK parameters, permeability optimized

Hydrocodone Intact Tablet
60 mg
In vitro dissolution profile (intact tablet) + model of “Hydrocodone Solution”

Hydrocodone Crushed Tablet
60 mg
In vitro dissolution profile (milled tablet) + model of “Hydrocodone Solution”

Hydrocodone Chewed Tablet
60 mg
In vitro dissolution profile (different gap sizes) + model of “Hydrocodone Solution”
Model Development and Validation

<table>
<thead>
<tr>
<th>Cmax (ng/ml)</th>
<th>AUC0-t (ng/ml×Hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Predicted</td>
</tr>
<tr>
<td>42.58</td>
<td>40.42</td>
</tr>
<tr>
<td>885.27</td>
<td>875.46</td>
</tr>
<tr>
<td>Observed</td>
<td>Predicted</td>
</tr>
<tr>
<td>71.11</td>
<td>70.88</td>
</tr>
<tr>
<td>646.36</td>
<td>647.18</td>
</tr>
<tr>
<td>Observed</td>
<td>Predicted</td>
</tr>
<tr>
<td>47.53</td>
<td>52.50</td>
</tr>
<tr>
<td>913.22</td>
<td>917.56</td>
</tr>
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</table>
Product-Specific Guidance (PSG)

• FDA publishes PSGs to facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval.

• PSGs describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent (TE = PE + BE) to specific reference listed drugs.

• For two products to be considered bioequivalent, there should be no significant difference in the rate and extent of absorption of the active moiety, which are usually measured by Cmax (the maximum drug concentration) and AUC (the area under the concentration-time curve), respectively.
Fasting comparative oral PK study of chewed drug products.

In addition to Cmax, AUC, partial AUCs e.g., AUC0-3hours and AUC0-4 hours as supportive data.
Virtual Comparative Oral Pharmacokinetic Study of Chewed Drug Products (TEST1/RLD)

<table>
<thead>
<tr>
<th>Cmax</th>
<th>AUC</th>
<th>pAUC 0-3 hour</th>
<th>pAUC 0-4 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMR</td>
<td>Upper 95%</td>
<td>GMR</td>
<td>Upper 95%</td>
</tr>
<tr>
<td>146.27</td>
<td>155.78</td>
<td>104.22</td>
<td>112.25</td>
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</tbody>
</table>
Virtual Comparative Oral Pharmacokinetic Study of Chewed Drug Products (TEST2/RLD)

<table>
<thead>
<tr>
<th>Cmax</th>
<th>AUC</th>
<th>pAUC 0-3 hour</th>
<th>pAUC 0-4 hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMR</td>
<td>Upper 95% Confidence Bound</td>
<td>GMR</td>
<td>Upper 95% Confidence Bound</td>
</tr>
<tr>
<td>98.69</td>
<td>105.75</td>
<td>96.20</td>
<td>106.48</td>
</tr>
</tbody>
</table>

www.fda.gov
Potential Challenges/Future Direction

• Validation of in vitro chewing method in combination with PBPK model to discriminate comparative oral chewing PK study

• Formulation development/Clinical study: NIPTE/Biopharma
Summary

• PBPK model for hydrocodone bitartrate ER tablet developed

• In vitro method of artificial chewing in combination with PBPK Modeling and Simulation can be helpful in predicting the in vivo behavior of hydrocodone bitartrate ER tablet after chewing followed by oral ingestion.

• Modeling & Simulation provides an important tool to support new and generic drug development:
  — Efficiency of clinical studies, test alternative scenarios
Thank You!


- For information about Model-Informed Drug Development Pilot Program (New Drug Development) please contact MIDD@fda.hhs.gov

- Alternative approaches to demonstrate bioequivalence: Applicants can submit their proposal through FDA’s Pre-ANDA program.

- Pre-ANDA Program Information: [https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm578012.htm](https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm578012.htm)

- For questions about submitting Pre-ANDA meeting requests for complex generic drug products online please contact PreANDAHelp@fda.hhs.gov
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Xiaoming Xu

[www.fda.gov/GDUFARegScience](http://www.fda.gov/GDUFARegScience)