Single- and Multiple-Dose Bioequivalence Studies for Oxycodone Extended Release 80 mg and 5 mg Tablet. Lessons learned at Biopharma Services Inc.

J. He, N. Gharavi, and F. Trabelsi
Biopharma Services Inc.

http://www.biopharmaservices.com

**PURPOSE**

The oxycodone extended release (ER) tablet (OxyContin® by Purdue Pharma L.P) provides long therapeutic duration for pain relief. The requirements of bioequivalence (BE) trials for generic drug submission for FDA and TPD require single-dose studies only, while EMA requires both, a multiple-dose study with the highest strength to demonstrate BE at steady-state, as well as a single-dose study.

**OBJECTIVE(S)**

Biopharma Services Inc. (BPSI) has conducted over 20 trials with doses ranging from 5 mg to 80 mg of oxycodone ER tablet using normal healthy volunteers (NHV). Four out of 20 studies were conducted as single-dose and multiple-dose trials using both the lowest (5 mg) and highest (80 mg) strengths. The objective of this presentation is to summarize pharmacokinetics (PK) and safety observations from in-house single-dose and multiple-dose trials.

**METHOD(S)**

- 4 pivotal studies
  - Randomized, two-sequence, two-treatment, two-period, crossover trials in NHV
  - 80 mg or 80 mg tablet strength (5 mg single-dose was fed study and no food effect was reported on PK of oxycodone)
  - Single-dose and Multiple-dose
    - Safety was monitored throughout the course of the trial by evaluating reported adverse events (AE), clinical laboratory test results, vital signs, and ECG findings
  - Blood samples for PK assessment were collected after oxycodone dosing
    - Single-dose sampling schedule up to 36 hours
    - Multiple dose sampling schedule (dosing interval 12 hours): Prior to the first dose of oxycodone administration; Pre-dose on Days prior to PK sampling day; On PK sampling day up to 12 hours
    - PK parameters such as maximum plasma concentration (C_{max}) and area under concentration-time curve (AUC) were determined.

**RESULT(S)**

- All successful BE studies with 90% confidence intervals of geometric mean ratios of C_{min} and AUC within 80.00% to 125.00%.
- The AEs observed in all single- and multiple-dose studies were either mild or moderate in nature.
- Rate of AE per subject was much higher in multiple-dose study (2.7%) than that from single-dose study (1%) for 80 mg strength.
- The percentage of moderate AEs was also higher in multiple-dose trial than it observed from single-dose trial of both 80 mg and 5 mg strengths

**CONCLUSION(S)**

- PK was well characterized with relatively low variability of oxycodone under both single-dose and multiple-dose conditions
- No accumulation of oxycodone after multiple-dose administration
- More AEs observed for 80 mg than that from 5 mg (either single-dose or multiple-dose conditions)
- More AEs observed when multiple doses was given comparing to AE seen from a single-dose studies
- With proper safety protection, multiple-dose of 80 mg of oxycodone clinical trial was successfully conducted in NHV
- Our experience showed 80 mg multiple-dose trial was safe in NHV and scientifically sound to be discriminative to determine BE

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**Table 1. Summary of studies conducted for single and multiple-dose administration**

<table>
<thead>
<tr>
<th>Study</th>
<th>Days of Dosing</th>
<th>Dose Titration</th>
<th>Dose Reduction</th>
<th>Washout</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg SD</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5 mg MD</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>5 mg SD</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Naltrexone given</td>
</tr>
<tr>
<td>5 mg MD</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Naltrexone given</td>
</tr>
</tbody>
</table>

**Table 2. Summary of AEs Observed from both Single and Multiple-Dose Administration of 5 and 80 mg Oxycodone**

<table>
<thead>
<tr>
<th>Study</th>
<th>Total AE</th>
<th>% AE/Subject</th>
<th>Mild AE</th>
<th>Moderate AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg SD</td>
<td>54</td>
<td>1</td>
<td>52</td>
<td>2</td>
</tr>
<tr>
<td>60 mg MD</td>
<td>94</td>
<td>2.7</td>
<td>86</td>
<td>8</td>
</tr>
<tr>
<td>5 mg SD</td>
<td>22</td>
<td>0.6</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>80 mg MD</td>
<td>39</td>
<td>1.1</td>
<td>36</td>
<td>3</td>
</tr>
</tbody>
</table>

**Figure 1. AUC (Mean +/- SD) from 80 mg Oxycodone after SD & MD Administrations**

**Figure 2. AUC (Mean +/- SD) from 5 mg Oxycodone after SD & MD Administrations**