A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution

Stephan Schmidt, B.Pharm., Ph.D., F.C.P.

Certara Professor
Associate Director Center for Pharmacometrics and Systems Pharmacology
Associate Professor & Associate Chair Department of Pharmaceutics (Lake Nona)
University of Florida at Lake Nona
A Model- and Systems-Based Approach to Efficacy and Safety Questions Related to Generic Substitution

Background:
• ~88% of prescription drugs filled in the U.S. are generic
• ~$1.68 Trillion of estimated cost savings for U.S. health system between 2005 and 2014
• U.S. FDA occasionally receives complaints about purported adverse events due to lack of efficacy or safety after switching from brand to generic
• Assessment of whether or not these complaints are real can be challenging

Research Strategy:
➢ To develop a quantitative and integrative approach that will separate post-marketing “signals from noise”
➢ If the “signal” is credible, develop a strategy using quantitative methods and modeling to provide insight into causal mechanisms

Lesko et al. accepted for publication in J Clin Pharmacol., 2017
Basu et al. accepted for publication in J Clin Pharmacol., 2017
5U01FD005210 – 04
Collaboration with Drs. Lesko (CPSP), Trame (CPSP), Vozmediano (CPSP), Bihorel (CPSP), Brown (COP-POP), Fang (FDA), Lionberger (FDA)
Analysis Workflow

ADE: FAERS, consumer complaints, www.peoplespharmacy.com, clinical studies, ISMP and other public databases

Confirmation – FAERS analysis

Replication – Truven® database

Enhanced FAERS analysis – Evidex™ by Advera Health

Confirm targets and pathways, and prediction of ADEs – MH Effect™

Causality of generic drug-AE pair

Prediction Modeling

PBPK Absorption Models: Sensitivity Analysis

PK/PD Models: Benefit and Risk

Model Interpretation and Report
Drugs and Formulations Selected To Demonstrate a Wide Range of Applications

**Case I:** anti-epileptic drugs considers BCS classification that can have a significant effect on absorption. BCS class II (carbamazepine, lamotrigine and phenytoin) and BCS class III (gabapentin and levetiracetam)

**Case II:** metoprolol XL examines a complex CR formulation to predict PK and PD profiles from a PSA and differences in *in vitro* dissolution

**Case III:** anticoagulants that belong to the same therapeutic class (DOACs) that are not yet available as generics to gain a mechanistic understanding of potential bioinequivalence
Signal Detection

- Formulation problems were reported within the first use of metoprolol XL and were public knowledge within 1-year of launch.
- Hypotheses for detecting formulation issues:
  - **Generic uptake/market share** will be decreased.
  - Patients will **discontinue** treatment and/or **switch back** to trade formulations at a higher rate.
  - **Event rates** for indicated conditions will be **elevated** for generic vs. trade formulations.
- To provide an active comparison:
  - **Amlodipine/Benazepril** was approved on the same date and launched at about the same with **no known formulation issues**.

### Clinical Event Rates

<table>
<thead>
<tr>
<th></th>
<th>Rate Ratio Generic vs. Trade (METO)</th>
<th>Rate Ratio Generic vs. Trade (AML O)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI</td>
<td>HF</td>
</tr>
<tr>
<td>ER Visits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>2.06</td>
<td>1.31</td>
</tr>
<tr>
<td>Secondary</td>
<td>2.42</td>
<td>1.20</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Primary</td>
<td>1.11</td>
<td>1.08</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Physiologically-Based Absorption Modeling

**In vitro and in silico dissolution testing**

**In vivo dissolution and in silico absorption modeling**

**In silico bioequivalence testing**

**Formulation**

**APPARATUS 2**

**The Gut**

**Advanced Compartment and Transit (ACAT) module in GastroPlus™**

Lesko et al. accepted for publication in *J Clin Pharmacol.*, 2017
Basu et al. accepted for publication in *J Clin Pharmacol.*, 2017

5U01FD005210 – 04

Collaboration with Drs. Lesko (CPSP), Trame (CPSP), Vozmediano (CPSP), Bihorel (CPSP), Brown (COP-POP), Fang (FDA), Lionberger (FDA)
Prediction of *In Vitro* Dissolution Based on the Formulation’s Composition & Manufacturing Conditions

*In vitro* Dissolution profiles

**Similarity (F2) test**

<table>
<thead>
<tr>
<th>Product</th>
<th>(% increase in K, actual K value)</th>
<th>F2</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>(0%, K = 0.006)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Test 1</td>
<td>(20%, K = 0.0072)</td>
<td>57</td>
<td>similar</td>
</tr>
<tr>
<td>Test 2</td>
<td>(40%, K = 0.0084)</td>
<td>44</td>
<td>different</td>
</tr>
<tr>
<td>Test 3</td>
<td>(60%, K = 0.0096)</td>
<td>37</td>
<td>different</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>(% increase in K, actual K value)</th>
<th>F2</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>(0%, K = 0.018)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Test 1</td>
<td>(20%, K = 0.0216)</td>
<td>52</td>
<td>similar</td>
</tr>
<tr>
<td>Test 2</td>
<td>(40%, K = 0.0252)</td>
<td>40</td>
<td>different</td>
</tr>
<tr>
<td>Test 3</td>
<td>(60%, K = 0.0288)</td>
<td>33</td>
<td>different</td>
</tr>
</tbody>
</table>

K: drug release rate constant, F2 ≥ 50 indicates similarity. Lower the F2 value, lower the similarity, whereas F2 = 100 indicates absolute similarity.
Effect of Drug Release on PK & Bioequivalence

K: drug release rate constant. The graphs in the left panel show the median (solid line), 5th and 95th percentiles (lower and upper dashed lines, respectively) of the concentration vs. time profiles (200 subjects). Bioequivalence (BE) was declared if a 90% confidence interval for the ratio of the geometric means of C\text{max} and AUC falls within 80 to 125% (green shaded area). The graphs in the right panel shows the BE testing using the more sensible parameter C\text{max}∗. BIN: bio-in-equivalence.
Effect of Drug Release on PD & Therapeutic Equivalence

PBPK/PD 200 mg

(a)  

c(d)  

(b)  

(c)  


c(d)  

K: drug release rate constant, The graphs show the median (solid line), 5th and 95th percentiles (lower and upper dashed lines, respectively) of the PD profiles. EHR: exercise-induced heart rate, \( \Delta \text{EHR} \): percentage reduction in EHR.

Reference for the target EHR zone: https://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm
Considering Anatomy & Physiology of the Heart

The underlying physiological mechanism of decreased HRV is likely to be an alteration in the cardiac sympathetic–parasympathetic balance, characterized by a relative sympathetic dominance probably secondary to reduced parasympathetic activity.
Ongoing Research: Heart Rate Variability (HRV) Data Used for Model Development


HRV analyses from 24-hour Holter data were divided into quartiles:
- quartile 1 (3 AM to 9 AM),
- quartile 2 (9 AM to 3 PM),
- quartile 3 (3 PM to 9 PM),
- quartile 4 (9 PM to 3 AM).

Fig. 1. (A) Comparison of high to total frequency variability ratios (normalized measures of parasympathetic activity) for immediate-release metoprolol (open circles) and extended-release metoprolol (black circles). Data are presented as mean ± SE; \( P < .05 \). (B) Comparison of low to total frequency variability ratios (normalized measures of sympathetic activity) for immediate-release metoprolol (open circles) and extended-release metoprolol (black circles). Data are presented as mean ± SE; \( P < .05 \). (C) Comparison of high to low frequency variability ratios (index of parasympathetic to sympathetic balance) for immediate-release metoprolol (open circles) and extended-release metoprolol (black circles). Data are presented as mean ± SE; \( P < .08 \).
Case Example: Metoprolol XL (BCS I, 2006)

- Indication: antihypertensive
- Generics: at least 3 from various manufacturers

Report from physician to FDA on 06-23-2014

Patient: male
Complaints: chest pains
Reaction: increase HR, increase BP, dizziness, migraine
AE resulted in: switch back to brand name product
Suspect Drug: metoprolol after substitution

https://www.nytimes.com/2014/06/24/health/warning-unheeded-heart-drugs-are-recalled.html
Lesko et al. accepted for publication in J Clin Pharmacol., 2017
Basu et al. accepted for publication in J Clin Pharmacol., 2017
5U01FD005210 – 04
Collaboration with Drs. Lesko (CPSP), Trame (CPSP), Vozmediano (CPSP), Bihorel (CPSP), Brown (COP-POP), Fang (FDA), Lionberger (FDA)
Stephan Schmidt:
sschmidt@cop.ufl.edu
Office: 407-313-7012
Cell: 352-408-2833