Use of Physiologically Based Pharmacokinetic Modeling as a Computational and Mathematical Tool to Evaluate the Switchability of Generic and Brand Name Products

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Introduction

- The Office of Generic Drugs (OGD) at FDA occasionally receives reports of potential product failure after switching from brand to generic product resulting in failure of efficacy or an adverse event. It is difficult to interpret these reports and confirm them.
- Bioequivalence in PK between drug products is typically evaluated using bioequivalence (BE) criteria [90% Confidence Interval (CI) for Area Under the Curve ($AUC_{0-\infty}$) and maximal concentration (C_{max})] as a surrogate for therapeutic equivalence[1].
- Physiologically-Based Pharmacokinetic (PBPK) modeling has gained popularity for dose selection, clinical trial design, and regulatory submissions (1). PBPK modeling integrates, on a mechanistic basis, the physiological parameters with the drug physicochemical properties. The main framework of PBPK models involve the drug specific, system specific and trial design parameters. These models can thus be used as a platform for evaluating the impact of pre-systemic changes on a drug's PK and absorption mechanisms.
- The main objective of this study is to evaluate the use of PBPK to determine the critical quality attributes of anti-epileptic drug (AED) that can possibly cause pharmacokinetic bioinequivalence (BIN) between generic and brand name products.

Methods

A step-wise approach was used for building and qualifying the PBPK models for AEDs and the sensitivity analysis.

Carbamazepine (CBZ), Lamotrigine (LMT) and Levetiracetam (LVT) were selected as candidate AEDs for representing a high, medium and low risk (2), respectively, due to switchability issues on pharmacokinetics leading to BIN of brand and generic products.

Individual PBPK models were developed in GastroPlus 9.0 for CBZ, LMT and LVT

- Characterizing the systemic clearance: *In vitro* K_m and V_{max} values obtained from literature were scaled to adult human K_m and V_{max} (IVIVE). *In vitro* dissolution data was used to simulate the pharmacokinetic profile *in vivo* wherever possible.
- Characterizing absorption related pre-systemic changes: Drug specific properties: pKa, log P, solubility System specific parameters: Anatomy, physiology, Gut ACAT™ model.
- Trial design parameters: Formulation, dose
- The model predictions were overlaid on observed plasma concentrations from the literature.
- External qualification of the PBPK models was performed by using a pharmacokinetic dataset from the literature which was not used for model building.

Sensitivity analysis was performed in GastroPlus 9.0:

- On selected formulation parameters and compound specific parameters within physiologically plausible limits.
- Formulation parameters: particle shape, particle radius, precipitation radius and particle density
- Compound specific parameters: solubility pH, solubility and precipitation time.
- To evaluate pharmacokinetic changes in the C_{max} and AUC (BE parameters) with probable differences in the brand and generic formulations. The pharmacokinetic parameters were considered statistically different from the reference product and considered to be BIN with respect to PK if they fell outside the BE limits of 0.8 – 1.25.

Results

Carbamazepine (High Risk)

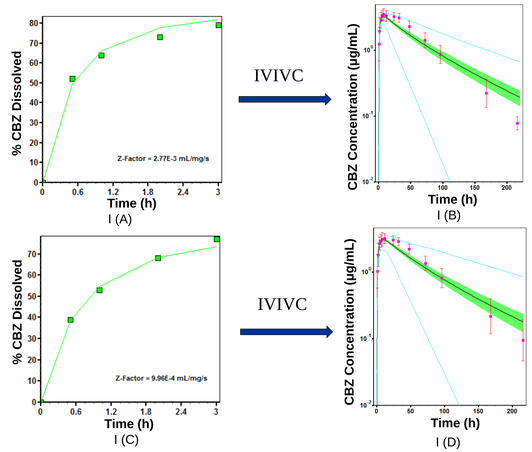

Figure I (A) (Reference) (C) (Test). *In vitro* dissolution model for IR CBZ. Solid dots: Observed dissolution profile; Green line: Fitted dissolution profile. Figure I (B) (D) PBPK models for IR CBZ; Solid dots: Observed plasma concentration; Black line: Simulated profile; Green band: 90 % C.I.; Blue line: 95 % Probability.

Lamotrigine (Medium Risk)

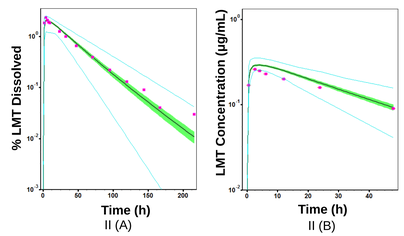

Figure II (A) (B) PBPK models for 200 mg tablet (A) and 25 mg capsule (B) LMT; Solid dots: Observed plasma concentration; Black line: Simulated profile; Green band: 90 % C.I.; Blue line: 95 % Probability.

Levetiracetam (Low Risk)

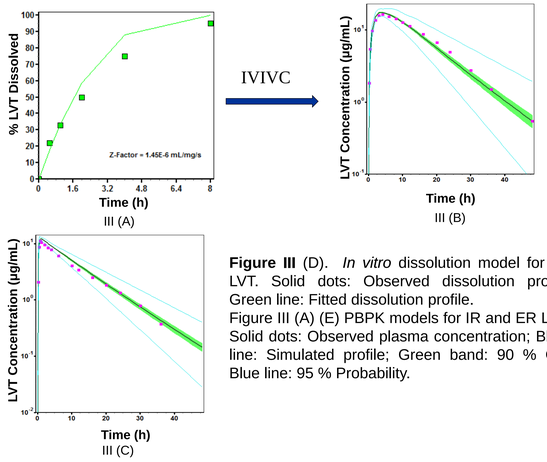

Figure III (D). *In vitro* dissolution model for ER LVT. Solid dots: Observed dissolution profile; Green line: Fitted dissolution profile.
Figure III (A) (E) PBPK models for IR and ER LVT; Solid dots: Observed plasma concentration; Black line: Simulated profile; Green band: 90 % C.I.; Blue line: 95 % Probability.

Sensitivity Analysis

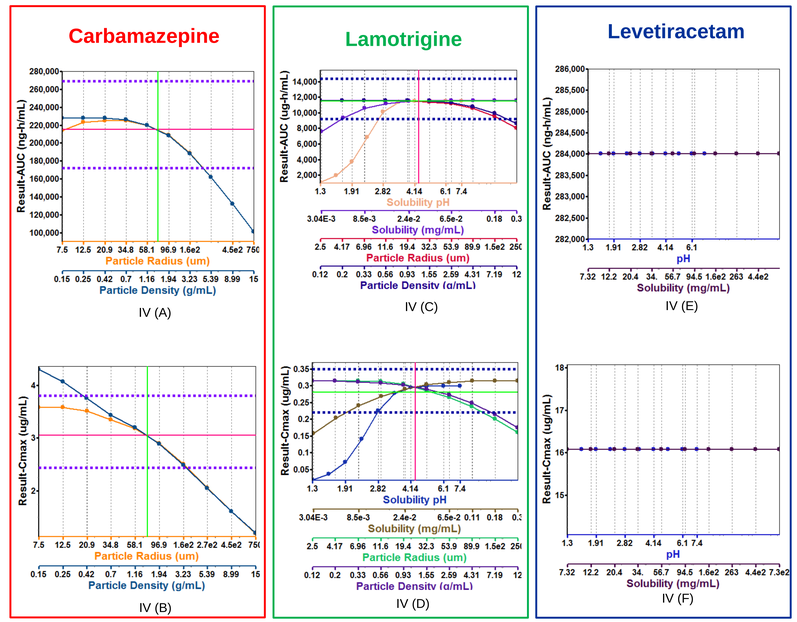

Figure IV Sensitivity analyses for effects of formulation and drug dependent parameters on C_{max} and AUC for CBZ (A), (B); LMT (C) (D); LVT (E) (F).

Conclusions

- BCS class II drugs (carbamazepine and lamotrigine) with low solubility could show PK BIN based on changes in particle radius, density and solubility. This PK BIN is not shown by BCS class I drug, levetiracetam. This finding is consistent with the high, medium and low risk categorization of AEDs
- We have demonstrated that PBPK models can provide a mechanistic understanding of critical drug and formulation quality attributes with respect to their influence on simulated PK profiles and bioequivalence parameters of AUC and C_{max}.
- This platform represents a valuable tool to explore the effects of quality attributes of AEDs and to generate hypothesis related to potential causes of BIN for future branded drugs coming off-patent.
- Simulated PK profiles from PBPK models should be confirmed with *in vivo* clinical testing.

References

1. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annual review of pharmacology and toxicology. 2011;51:45-73.
2. Chaplin, Steve. "CHM guidance on switching between AED formulations."*Prescriber* 25.11 (2014): 31-32.

Acknowledgement

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