U.S. FOOD & DRUG ADMINISTRATION

Assessment of the Impact of Non-Comparable In Vitro Alcohol Dose Dumping Release on Systemic Exposure Using PBPK Absorption Modeling for Topiramate Extended-Release Capsules

Yi-Hsien Cheng, Fang Wu, Youssef Mousa, Liang Zhao, Lanyan (Lucy) Fang

Division of Quantitative Methods and Modelling (DQMM), Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), Silver Spring, MD 20993

BACKGROUND

Topiramate extended-release (ER) capsules is indicated for epilepsy control and preventive treatment of migraines. Due to concerns of alcohol dose dumping (ADD), additional dissolution testing using various ethanol concentrations in pH 1.1 medium is recommended for topiramate ER capsules. This study used a physiologically based pharmacokinetic (PBPK) absorption model to assess whether the non-comparable in vitro dissolution results observed at pH 1.1 with 20% ethanol, as opposed to 5% or 40% ethanol, would impact bioequivalence (BE) determination between test product and reference listed drug (RLD).

METHODS

Physicochemical properties were obtained based upon literature and ADMET Predictor™ from the GastroPlus™ software (Version 9.8.2, Simulations Plus Inc., CA, USA). Disposition parameters were estimated from PK data in healthy subjects following intravenous infusion with 100 mg topiramate using PKPlus™. Permeability parameter (Peff) was estimated using PK data obtained from healthy subjects following oral administration of 50 and 100 mg immediate release (IR) tablets. Dissolution data at pH 1.1, pH 6.8, and pH 7.5 and developed bi-phasic dissolution profiles (i.e., drug release for 1 hour at pH 1.1 and release at pH 6.8 or pH 7.5 afterwards) were incorporated in the PBPK model to predict PK profiles following administration with test product and RLD of 200 mg topiramate ER capsules under fasted conditions. Dissolution data and PK data of RLD of other strengths (50, 100, and 200 mg) were used to further validate the PBPK model. PBPK modeling and virtual BE (VBE) simulations were conducted to evaluate the impact of the non-comparable in vitro ADD release on the predicted systemic exposure, and overall BE determination.

RESULTS

The oral PBPK model incorporating in vitro dissolution data at pH 6.8 and pH 7.5, accurately predicted plasma profiles for 200 mg topiramate ER capsules under fasted conditions with prediction errors (PE) of <20% (**Figure 1**). In addition, the PBPK model incorporating dissolution data at pH 6.8 and pH 7.5 adequately captured additional PK profiles of RLD with PE of <20%, suggesting appropriate model validation (**Figure 2**).

PBPK modeling and virtual BE simulation to evaluate the impact of non-comparable in vitro drug release on drug exposure in vivo

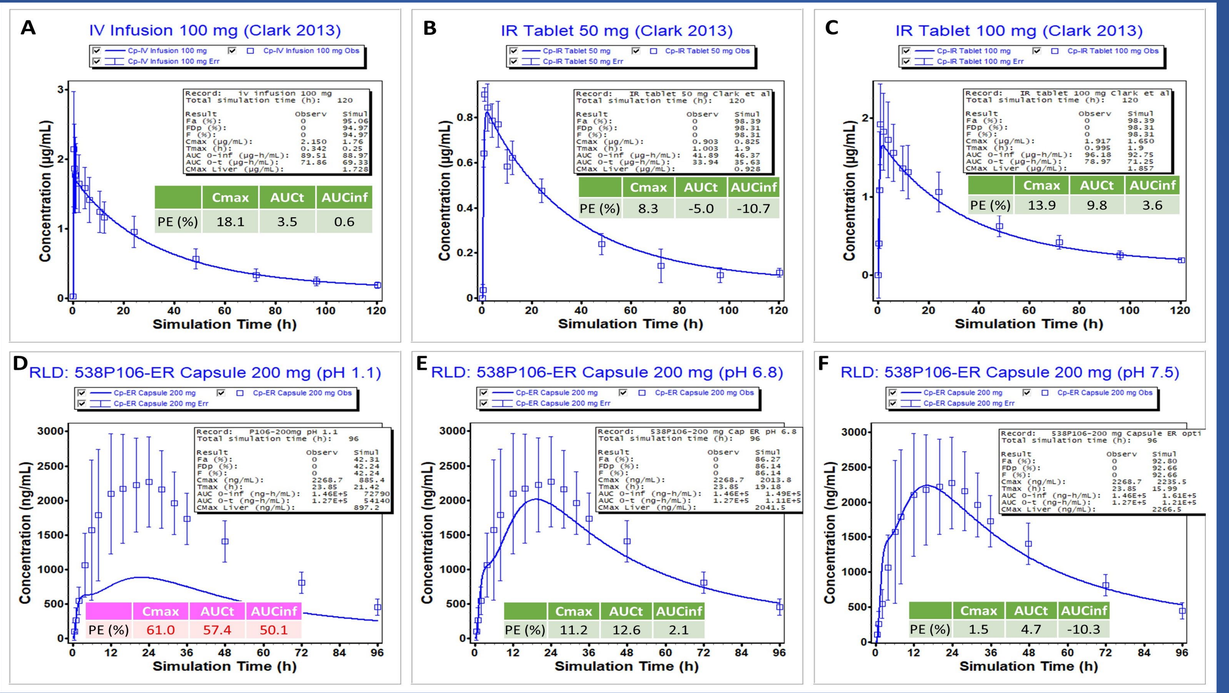

Figure 1. Model development: Observed and simulated PK profiles for topiramate using developed PBPK model in healthy subjects following administration of (A) 100 mg IV infusion, (B) 50 mg IR tablet, (C) 100 mg IR tablet, and 200 mg ER capsule with integration of in vitro dissolution data obtained at (D) pH 1.1, (E) pH 6.8, and (F) pH 7.5. Dissolution data obtained at pH 6.8 and 7.5 were biopredictive of PK profiles of RLD.

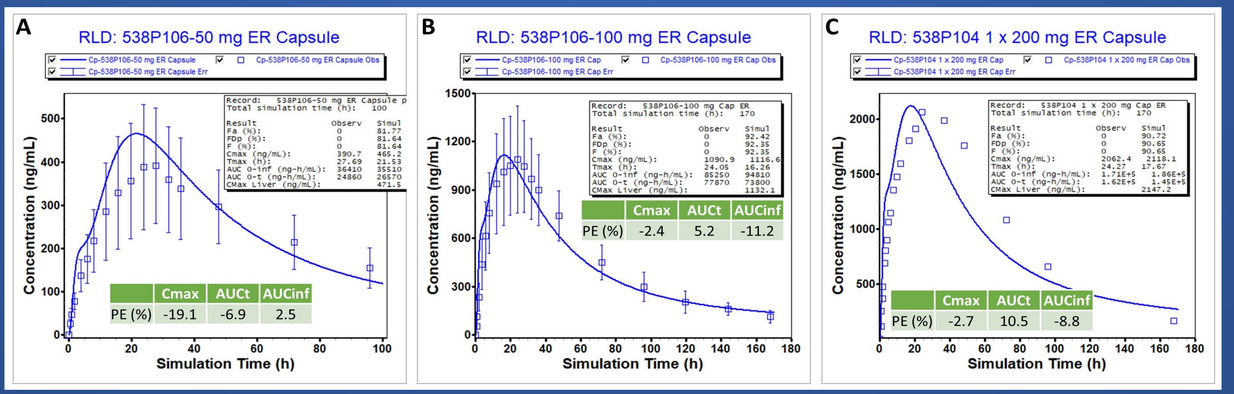

Figure 2. Model validation: PBPK model prediction versus observed PK data of RLD in healthy subjects administered with (A) 50 mg, (B) 100 mg, and (C) 200 mg topiramate ER capsule, respectively.

RESULTS (cont.)

Despite the fact that test product showed faster in vitro drug release at pH 1.1 with 20% ethanol, validated PBPK model predicted that test product of 200 mg topiramate ER capsules is bioequivalent to the RLD under in vivo conditions (**Figure 3A**). Moreover, by incorporating the developed bi-phasic dissolution profiles mimicking real drug release in vivo, VBE simulation demonstrated that there is a low risk of non-BE between the test and RLD product of 200 mg topiramate ER capsules (**Figure 3B and 3C**). The non-comparable in vitro ADD release results in pH 1.1 medium with 20% ethanol does not lead to differences in the predicted in vivo systemic exposure between the test product and RLD, thus indicating a low risk of bioinequivalence (**Figure 3**).

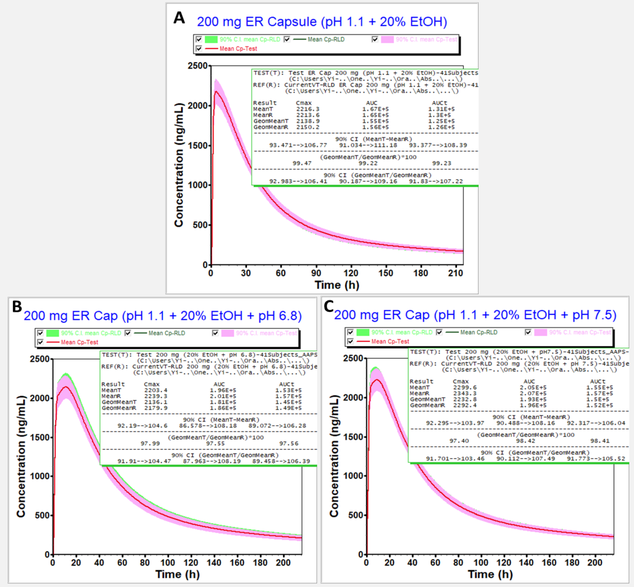

Figure 3. Representative VBE simulation results integrating (A) dissolution data at pH 1.1 with 20% ethanol and developed bi-phasic dissolution profiles, i.e., drug release in 1 hour at pH 1.1 with 20% ethanol and release at (B) pH 6.8 or (C) pH 7.5 afterwards.

CONCLUSION

The PBPK absorption model adequately predicted various topiramate PK profiles. Moreover, PBPK modeling and VBE trial results suggest that the test product and RLD have comparable PK parameters although faster release of test product was observed in the in vitro ADD study with 20% ethanol.

Disclaimer: This poster represents the views of the presenters only and should not be construed to represent FDA's views or policies.

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